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Article

# New Crystalline Salts of Nicotinamide Riboside as Food Additives

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**Abstract:** NR<sup>+</sup> is a highly effective vitamin B<sub>3</sub> type supplement due to its unique ability to replenish NAD<sup>+</sup> levels. While NR<sup>+</sup> chloride is already on the market as a nutritional supplement, its synthesis is challenging, expensive, and low yielding, making it cumbersome for large-scale industrial production. Here we report the novel crystalline NR<sup>+</sup> salts, D/L/DL-hydrogen tartrate and D/L/DL-hydrogen malate. Their high-yielding, one-pot manufacture does not require specific equipment and is suitable for multi-ton scale production. These new NR<sup>+</sup> salts seem ideal for nutritional applications due to their bio-equivalence compared to the approved NR<sup>+</sup> chloride. In addition, the crystal structures of all stereoisomers of NR<sup>+</sup> hydrogen tartrate and NR<sup>+</sup> hydrogen malate and a comparison to the known NR<sup>+</sup> halogenides are presented.

**Keywords:** nicotinamide riboside; B<sub>3</sub> supplement; NR<sup>+</sup> salts; crystal structures; salt screening

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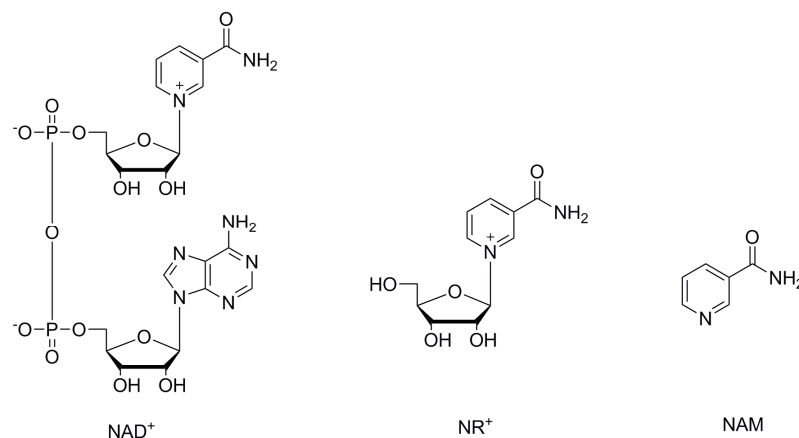


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## 1. Introduction

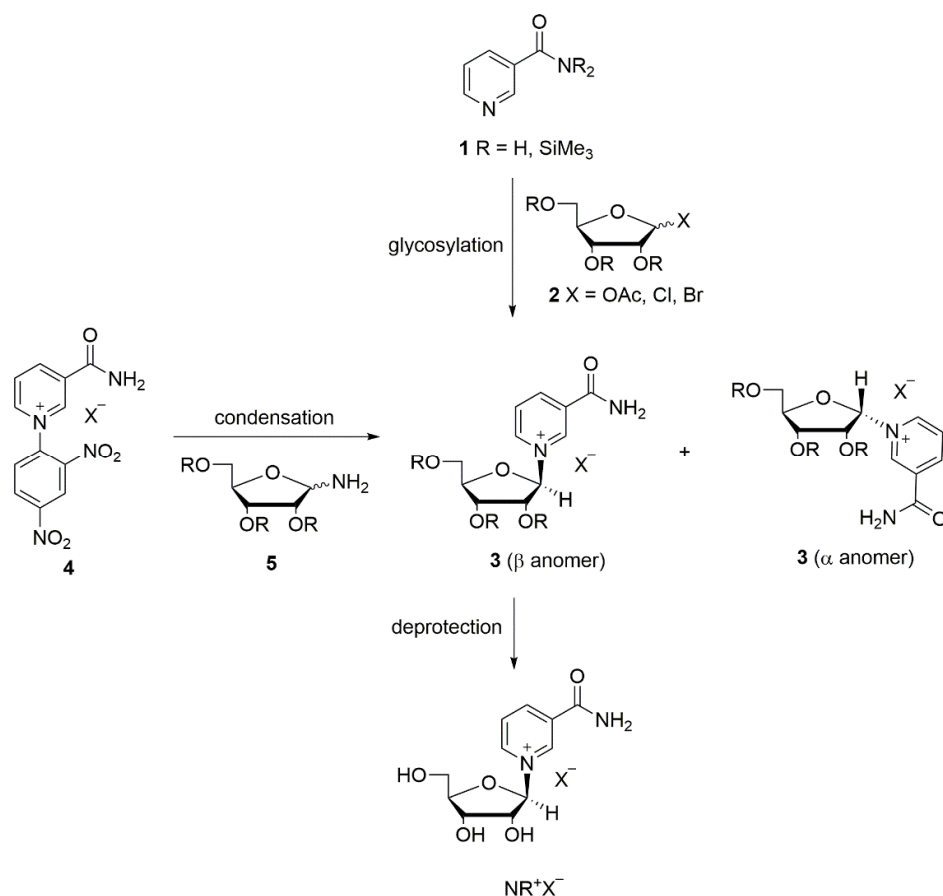
Nicotinamide adenine dinucleotide (NAD<sup>+</sup>) (Figure 1) is a redox cofactor for hydride transfer enzymes such as oxidoreductases, with a crucial role in cell metabolism and in the response to oxidative stress [1–4]. Additionally, NAD<sup>+</sup> takes part in vital processes not involving hydride transfer such as signaling [1,5], post-translational modification [1,3,6], transcription regulation [1], DNA repair, circadian activity modulation [7,8], and in the regulation of protein–protein interactions. Decreased levels of NAD<sup>+</sup> are associated with the nuclear and mitochondrial dysfunctions associated with aging [1,2,4,7,9,10] as well as pathophysiological conditions such as ischemia [11–13], obesity [2,4,14–16], type 2 diabetes [2,17–19], metabolic syndrome [2,4,19], non-alcoholic fatty liver disease [2,19], and neurodegenerative disorders [2,4,20,21]. The understanding of the mechanisms and roles of decreased NAD<sup>+</sup> levels during aging and age-related diseases is of great interest to the scientific community. Numerous studies have been published, many of them showing that supplementing NAD<sup>+</sup> can increase its bioavailable levels and have beneficial effects [1,2,4,7,9,10]. Increased levels of NAD<sup>+</sup> can be achieved by supplementation with its precursors, and have great potential in the treatment of pathophysiological conditions involving decreased NAD<sup>+</sup> levels [4,9,22–24]. For this reason, the scientific community has recently been focusing on the roles of NAD<sup>+</sup> key precursors, with emphasis on nicotinamide riboside (NR<sup>+</sup>) (Figure 1) [11,22–24]. NR<sup>+</sup> is a niacin equivalent and a form of vitamin B<sub>3</sub> naturally present in milk [25,26]. The recommended daily intake (RDI) or allowance (RDA) for adults is about 20 mg (equivalent to 0.2 mmol)[27] and it is commercially available as an additive in nutritional supplements and pharmaceutical compositions

[23,28,29].  $\text{NR}^+$  is converted into  $\text{NAD}^+$  by  $\text{NR}^+$  kinase [30], or by the nucleoside phosphorylase and the nicotinamide (NAM) (Figure 1) salvage pathway [9]. When orally supplemented, a preventive and therapeutic effect in numerous diseases has been observed in association with increased  $\text{NAD}^+$  levels [9,11,22–24,30,31].  $\text{NR}^+$  is preferred over other  $\text{NAD}^+$  precursors because its use is not related to serious side effects or flushing, as has been observed with other  $\text{NAD}^+$  precursors [26,32].



**Figure 1.** Structures of  $\text{NAD}^+$ ,  $\text{NR}^+$  and NAM.

The synthesis and manipulation of  $\text{NR}^+$  salts is challenging due to the relatively labile glycosidic bond compared to other nucleosides [33]. Until now, only the bromide and the chloride of  $\text{NR}^+$  were known as crystalline salts, and only recently have the crystal structures of  $\text{NR}^+$  bromide, chloride, and other non-phosphate ester derivatives been elucidated [34]. Due to its toxicity, the bromide salt is unsuitable as a food supplement. The chloride salt of  $\text{NR}^+$  instead has been generally recognized as safe (GRAS) by the FDA, and numerous studies in humans support this statement. Therefore, the chloride salt of  $\text{NR}^+$  is currently commercially available as a dietary supplement [28,35–41]. Several synthetic routes towards  $\text{NR}^+$  salts have been reported with two main approaches. The first is the glycosylation of NAM or its derivatives **1** with halosugars or peracylated ribofuranoses **2**, forming the  $\text{NR}^+$  salt via its acylated intermediate **3**. The second approach involves the condensation reaction between *N*-(2,4-dinitrophenyl)-3-carbamoylpyridinium salts **4** and derivatives of D-ribofuranosylamine **5** (Scheme 1) [33]. The synthesis of  $\text{NR}^+$  often achieves poor stereoselectivity, with formation of a mixture of  $\alpha$  and  $\beta$   $\text{NR}^+$  anomers. Since only the  $\beta$  form is biologically active, high stereoselectivity towards the  $\beta$   $\text{NR}^+$  anomer is highly desirable [33].



**Scheme 1.** Main approaches for the  $\text{NR}^+$  synthesis. Adapted from Makarov and Migaud [33].

In the first reports describing reactions between NAM and halosugars **7**, Todd and coworkers [42,43] obtained triacetylated or tribenzoylated  $\text{NR}^+$  salts **8** in anhydrous acetonitrile, followed by deprotection in methanolic ammonia at low temperature (Scheme 2A) [33,42,43]. Mikhailopulo et al. reported the synthesis of the acetylated and benzoylated bromide intermediates **8** in liquid  $\text{SO}_2$  (Scheme 2); however this solvent is not suitable for large-scale industrial production [44]. Lee et al. investigated the anomeric ratio obtained in the synthesis of acylated or benzoylated bromosugars **7** via bromination with  $\text{HBr}$ , which were then reacted with NAM in the glycosylation step (Scheme 2A). A 1.5:1 mixture of  $\beta/\alpha$  anomers was obtained from the acylated sugar, while a 10:1 mixture was obtained with the benzoylated sugar [45].

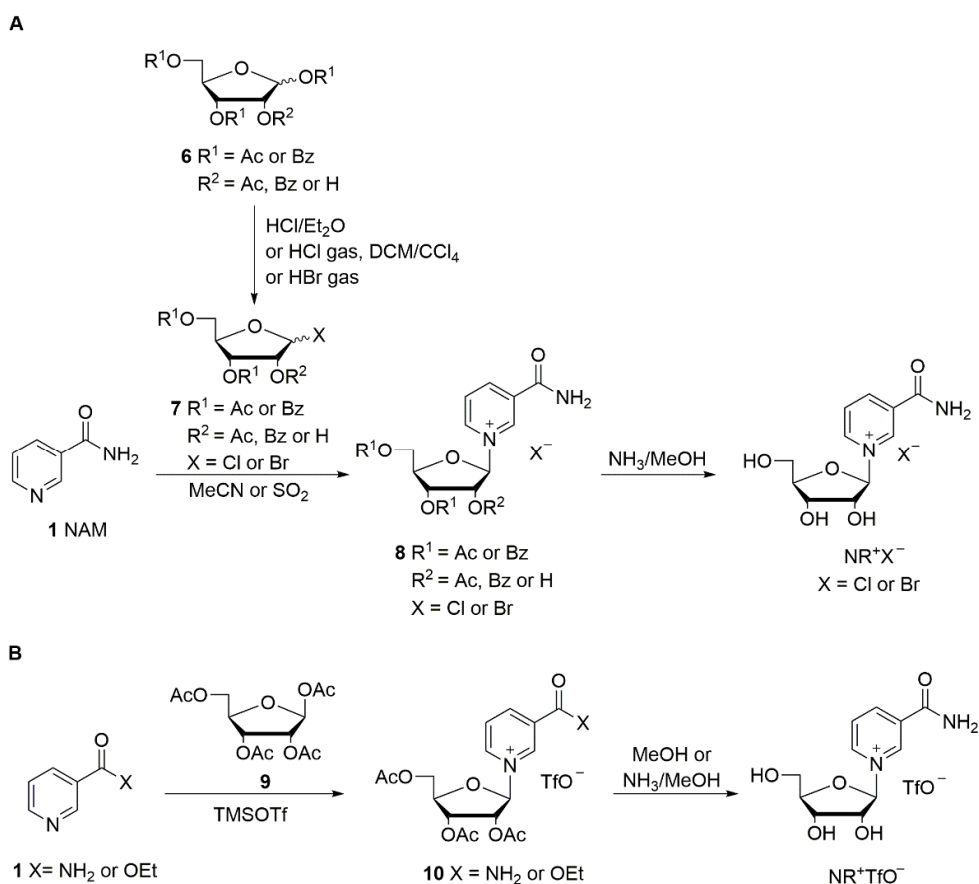
Although the yields and stereoselectivity of  $\text{NR}^+$  bromide were generally improved compared to the chloride salt [33,45–48], the bromide is unsuitable for biological applications due to its toxicity. Therefore, an ion exchange step to the chloride is required to obtain a salt with a pharmaceutically acceptable counter ion. The conversion of  $\text{NR}^+$  bromide to  $\text{NR}^+$  chloride via ion exchange methods is not economically attractive for large quantities due to its low exchange capacity. For a complete exchange, either a large exchanger quantity with a correspondingly large amount of solvent is required, or a time-consuming multiple-step process execution is necessary. Moreover, the energy-intensive removal of large quantities of solvent promotes the undesired hydrolysis of  $\text{NR}^+$ .

Recently Migaud et al. [47] reported the synthesis of triacetylated  $\text{NR}^+$  chloride in a 6:4 mixture of  $\beta/\alpha$  anomers, with the pure  $\beta$  anomer isolated simply by filtration and washing with acetone. The best deacetylation conditions were reported to be an anhydrous methanolic solution of  $\text{HCl}$ . Nevertheless, the use of hydrogen chloride, either gaseous or produced in situ, present some issues when scaling-up for industrial production.

The use of gaseous hydrogen chloride is expensive in terms of apparatus, while its production in situ requires the use of highly reactive and corrosive reagents which are potential sources of danger.

An alternative synthetic route involves the Hilbert–Johnson method, in which silylated heterocyclic bases are glycosylated with acylated (halo)ribofuranoses in the presence of a Friedel–Crafts catalyst, such as TMSOTf [33]. Tanimori et al. [49] reported the glycosylation of NAM with 1,2,3,5-tetra-*O*-acetyl- $\beta$ -D-ribofuranose **9** in acetonitrile at room temperature in the presence of 7.3 equivalents of TMSOTf. The formed acetylated NR<sup>+</sup> triflate salt **10** was deprotected by methanolysis (Scheme 2B). Improved methods have since been reported by Franchetti et al. [50] and Dellinger et al. [51].

Since the triflate is not a pharmaceutically acceptable counter ion, ion exchange is required. This can be achieved by washing with saturated solutions of sodium chloride [52], or by employing ion-exchange resins [53]. Sauve et al. [54–56] reported a convenient two-step, one-pot synthetic route consisting of the coupling of ethyl nicotinate and the acetylated sugar **9** in the presence of one equivalent of TMSOTf in dry dichloromethane. Successive deacetylation and hydrolysis of the ethyl ester was performed in one step with methanolic ammonia (Scheme 2B). Felczak [57] described the synthesis of pharmaceutically acceptable salts of NR<sup>+</sup> starting from silylated NAM and the chlorosugar. However, NR<sup>+</sup> chloride was isolated after deacetylation as a 3:2  $\beta/\alpha$  mixture in 38% yield only.



**Scheme 2.** Adapted from Makarov and Migaud [33].

In summary, the production of NR<sup>+</sup> chloride on the industrial scale is associated with relatively high costs due to the complex and process-intensive synthesis, low yields, poor stereoselectivity, and the use of hazardous or expensive starting materials. The synthesis

of the bromide salt is easier, affords higher yields and has better stereoselectivity. However, an additional ion-exchange step is required, which is not ideal for a large-scale synthetic procedure. The discovery of a scalable and efficient synthetic procedure of NR<sup>+</sup> pharmaceutically acceptable salts is of great interest from the nutrition perspective and would achieve a very significant market volume comparable to vitamin B12, once a suitable process of manufacturing has been established.

## 2. Materials and Methods

### 2.1. Chemical Synthesis

All reactions were carried out in closed glass vessels under atmospheric pressure without special need for an inert atmosphere. Unless otherwise stated, there was no need for special precautions to exclude moisture. Reagents and solvents were used as purchased without further purification. Proton and carbon NMR spectra for all compounds were acquired on a Bruker Avance III HD 400 MHz spectrometer (Bruker Switzerland AG, Faellanden, Switzerland) at room temperature. Chemical shifts were directly referenced to the residual non-deuterated solvent signal. Ion Chromatography (IC) was performed on a Dionex ICS-2000 System (Thermo Fisher Scientific AG, Reinach, Switzerland). Thin layer chromatography was performed using Merck silica gel 60 F254 plates (Merck KGaA, Darmstadt, Germany) with a solvent system *n*-butanol/water/acetic acid 5:3:2 and visualized with UV light. Melting points (Mp) were measured on a Büchi B-540 melting point apparatus (Büchi Labortechnik AG, Flawil, Switzerland). The synthetic procedures are reported in the Supplementary Information.

### 2.2. Single Crystal Growth Experiments

Single Crystal Growth experiments were attempted with nicotinamide- $\beta$ -D-ribose D-hydrogen tartrate, nicotinamide- $\beta$ -D-ribose L-hydrogen tartrate, nicotinamide- $\beta$ -D-ribose L-hydrogen malate, and nicotinamide- $\beta$ -D-ribose D-hydrogen malate, all provided in powder form by Biosynth Carbosynth (Staad, Switzerland). Each nicotinamide riboside derivate was left to crystallize using 7 different crystallization trials for a total of 28 crystallization setups. Four different methods were used: vapor diffusion, controlled cooling, under oil crystallization, and combined heating with anti-solvent precipitation.

Vapor Diffusion was trialed for all the nicotinamide riboside derivatives [58]. For each setup, a saturated solution of the compound in 1 mL of methanol (MeOH) was made and filtered. The solution was transferred to a thin vial. A larger scintillation vial was then filled with about 3 mL of the anti-solvent, tetrahydrofuran (THF). The thin vial was then gently placed inside the larger, out vessel, sealed off, and left to crystallize. A second trial series was performed using acetonitrile (MeCN) as the solvent and tetrahydropyran (THP) as the anti-solvent. When the crystals had formed, the vessel was opened, and a single crystal was removed for the single crystal X-ray diffraction analysis. With this method, crystals of nicotinamide- $\beta$ -D-ribose D-hydrogen tartrate **11a** were obtained by vapor diffusion of THF into MeOH; the crystals are shown in Figure S1A, Supplementary Materials.

Controlled cooling was trialed for all the nicotinamide riboside derivatives. A saturated solution of each compound in MeOH, MeCN, and a 4:1 ratio of MeOH to water were separately produced and filtered. An amount of 200  $\mu$ L of each of the 12 solutions was transferred to a small, liquid sampling vial and capped off. The trials were set in a Styrofoam box to slow the rate of cooling and placed in the refrigerator. At regular intervals, the crystallization setups were checked. When crystals had formed, the vial was opened, and a single crystal was selected and removed for the single crystal X-ray diffraction analysis. Using this method, crystals of nicotinamide- $\beta$ -D-ribose D-hydrogen tartrate monohydrate **11b** and L-hydrogen tartrate **12** respectively, were both obtained from the 4:1 MeOH to water solvent mixture; the crystals are shown in Figures S1B and C, Supplementary Materials.

Under oil crystallization was trialed for all the nicotinamide riboside derivatives [59]. A saturated solution of each compound in either water or a 4:1 ratio MeOH to water was produced separately and filtered. Eight wells were filled with 100  $\mu$ L of silicone oil. 5  $\mu$ L of the saturated solution was then added to each well. Using this method, no crystals were obtained.

Nicotinamide- $\beta$ -D-ribose L-hydrogen malate **13** and nicotinamide- $\beta$ -D-ribose D-hydrogen malate **14** were crystallized by thermal crystallization and cooling. Compound **13** was crystallized by dissolving 100 mg of the salt **13** in 76  $\mu$ L of double distilled water at 37 °C maintained by a water bath, while stirring. The stirring was turned off and a total of 200  $\mu$ L of ethanol was added in four portions over a period of half an hour. The vial was taken out of the water bath and after 20 min, large colourless crystals had formed. Compound **14** was crystallized by dissolving 50 mg of the salt **14** in 102  $\mu$ L of double distilled water at 37 °C maintained by a water bath, while stirring. The heating of the water bath and the stirring were turned off and 204  $\mu$ L of ethanol was added. After two days, large colourless crystals had formed.

### 2.3. X-Ray Single Crystal Diffraction

Crystallographic data were collected at 160.0(1) K on a Rigaku-Oxford Diffraction XtaLAB Synergy-S dual source diffractometer (Rigaku Europe SE, Neu-Isenburg, Germany). This is a kappa-axis four-circle goniometer with a Dectris Pilatus3 R 200K HPC (Hybrid Photon Counting) detector (DECTRIS Ltd., Baden-Daettwil, Switzerland) and Cu and Mo PhotonJet microfocus X-ray sources. Suitable crystals were covered with oil (Infiniteum V8512, formerly known as Paratone N; Infiniteum International Ltd., Abingdon, United Kingdom), placed on a nylon loop mounted on a CrystalCap Magnetic<sup>TM</sup> pin (Hampton Research, Aliso Viejo, CA, USA), and immediately transferred to the diffractometer. The program suite CrysAlisPro was used for data collection, numerical and multi-scan absorption correction as well as data reduction [60]. The structures were solved with the dual-space algorithm using SHELXT [61] and refined by the full-matrix least-squares methods on  $F^2$  with SHELXL-2018 [62] using the Olex2 GUI [63]. The graphical output was produced with the help of the program Mercury [64]. The calculation of the conformation of the ribose rings was done with the help of the program Platon [65] following the description reported by Saenger [66]. CCDC entries 2048059–2048063 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/structures](http://www.ccdc.cam.ac.uk/structures).

### 2.4. Stability Studies of NR<sup>+</sup> Salts 1–4

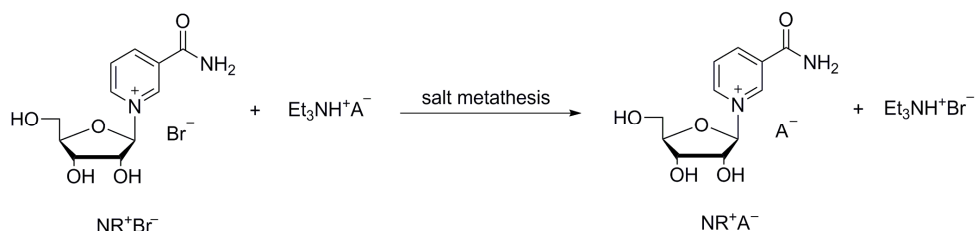
The stability of 1 mg/mL aqueous solutions of NR<sup>+</sup> hydrogen tartrate, hydrogen malate, chloride and bromide was tested by HPLC analysis using a Thermo Fischer Ultimate 3000 instrument (Thermo Fisher Scientific AG, Reinach, Switzerland); Column: Interchim Uptisphere SCX 120 Å, 150 x 4.6 mm, 3  $\mu$ M; Mobile phase: 100 mM NH<sub>4</sub>HCOO<sup>−</sup> aqueous Buffer, pH 3.20, MeCN; Method: isocratic 70% MeCN; Detection: UV 254 nm; Flow rate: 1.50 mL/min; Column Oven Temperature: 30 °C; Injection Volume: 10  $\mu$ L; Run time: 15 min). The samples were run in phosphate buffer at various acidic and neutral pHs (pH 2.5, pH 3.5, pH 4.5, pH 7.0, 0.75% hydrochloric acid), and at different temperatures (5 °C, RT, 40 °C) over time (daily/weekly). The relative peak area of NAM (retention time 1.7 min), formed by degradation of the NR<sup>+</sup> salt, was used as an index of stability.

## 3. Results

In order to overcome the above-described limitations regarding the synthesis of NR<sup>+</sup> salts, we investigated alternatives to chloride as the NR<sup>+</sup> counterion. Our aim was to introduce new pharmaceutically acceptable NR<sup>+</sup> crystalline salts, which would be better suited to industrial manufacturing, with lower production costs and easier purification to

pharmaceutical standards compared to the commercially available NR<sup>+</sup> chloride. Our initial goal was to screen, identify, and isolate new crystalline forms of NR<sup>+</sup> salts. Once such compounds were identified, we then searched for a cheap, easily accessible synthetic methodology well suited to large-scale production.

Initially, we screened different NR<sup>+</sup> salts searching for new stable and crystalline forms, without using time-consuming and unsuitable hydrolysis-prone ion exchange procedures. These NR<sup>+</sup> salts were initially prepared by salt metathesis from NR<sup>+</sup> bromide and triethylammonium salts of various acids (Scheme 3). The synthesis of neutral salts and acidic salts was attempted.



**Scheme 3.** Synthesis of new NR<sup>+</sup> salt via salt metathesis from NR<sup>+</sup> bromide and triethylammonium salts.

### 3.1. Preparation of NR<sup>+</sup> Neutral Salts

When the triethylammonium salts, which are highly soluble in methanol, were added to a suspension of NR<sup>+</sup> bromide in methanol, a clear solution was obtained upon gentle heating. By decreasing the temperature of the solution, usually no solid crystallized, presumably because the dissolved NR<sup>+</sup> bromide increased the polarity of the supersaturated solution. Crystallization of the undesired bromide salt was observed only with the formate, salicylate, and maleate salts. Additionally, we observed that in the presence of longer chain alcohols, NR<sup>+</sup> bromide crystallized with lactate, malonate, methane sulfonate, and sorbate salts. Thus, these salts are either more soluble in methanol compared to the bromide, or not able to form crystals at all. No solid or waxy solid was obtained with benzenesulfonate, fumarate, or succinate.

We expected NR<sup>+</sup> to be most stable in solutions of the neutral salts of strong mineral acids such as sulfuric acid, or strong organic acids such as benzenesulfonic and methanesulfonic acid. However, in the presence of the corresponding triethylammonium salts we observed no formation of crystals. Carbonic acid salts were not stable towards hydrolysis due to their weakly basic properties and therefore no crystallization was expected.

Furthermore, only a small selection of the desired new salts formed by metathesis precipitated as stable solids by adding the obtained solution in methanol to longer chain alcohols, such as *n*-propanol, *n*-butanol, and isopropanol. These are the NR<sup>+</sup> salts of L-ascorbic acid, citric acid, D-glucuronic acid as well as of L-malic and L-tartaric acid. These amorphous solids were purified by trituration from alcohols.

The described results are reported in Table 1.

**Table 1.** Salt metathesis results with NR<sup>+</sup> neutral salts.

A in Et <sub>3</sub> N·A	NR <sup>+</sup> Br <sup>−</sup> (g)	H <sub>2</sub> O (mL)	MeOH (mL)	S/D*	Et <sub>3</sub> N·A (mL)	Solvent Added (mL)	NR·A (g)	NR <sup>+</sup> Br <sup>−</sup> (g)	Yield %
L-Ascorbate	5.0	3	10	D	16	375 EtOH	3.45	-	54
Benzenesulfonate	0.56	0.4	1	D	1	-	-	-	0
Citrate	9.0	-	18 (DMSO)	D	73	1125 iPrOH	6.32	-	75
Formiate	10.0	-	25	S	12.5	-	-	6.21	0
Fumarate	0.50	0.3	1	S	0.5	-	-	-	0



D-Glucuronate	5.0	3	10	D	11.3	455 <i>n</i> -BuOH	6.64	-	99
Lactate	5.80	-	20	S	10	400 <i>i</i> PrOH	-	4.27	0
L-Malate	5.0	-	15	S	10	280 <i>i</i> PrOH	4.51	-	100
Maleate	0.94	-	1	S	1	-	-	0.24	0
Malonate	7.10	4.3	14	D	7.3	350 <i>i</i> PrOH	-	5.75	0
Methane sulfonate	0.62	0.4	1	D	1	24 <i>n</i> -BuOH	-	0.23	0
Salicylate	2.75	-	9	S	5	-	-	1.73	0
Sorbate	2.90	1.5	5	D	5	100 Dioxane	-	1.93	0
Succinate	0.48	0.3	1	S	0.5	-	-	-	0
L-Tartrate	9.65	5.8	20	D	10	500 EtOH	8.06	-	85

\* S = suspended, D = dissolved.

### 3.2. Preparation of NR<sup>+</sup> Acidic Salts

The synthesis of NR<sup>+</sup> salts of acidic dicarboxylates was investigated following a similar procedure used for the neutral NR<sup>+</sup> salts. In the presence of acidic salts of di- or tri-carboxylic acids, NR<sup>+</sup> proved to be more stable, but in most cases the NR<sup>+</sup> bromide crystallized.

NR<sup>+</sup> bromide crystallized with the acidic carboxylates of citrate, fumarate, maleate, malonate, mercaptosuccinate,  $\alpha$ -ketoglutarate, oxaloacetate, oxalate, succinate, and tartrate. NR<sup>+</sup> dihydrogen citrate and meso-hydrogen tartrate formed as unstable solids when the metathesis solution was dropped into isopropanol and ethanol, respectively. To our surprise, NR<sup>+</sup> crystalline salts formed with D, L, DL hydrogen malate and D, L, DL hydrogen tartrate. The described results are reported in Table 2.

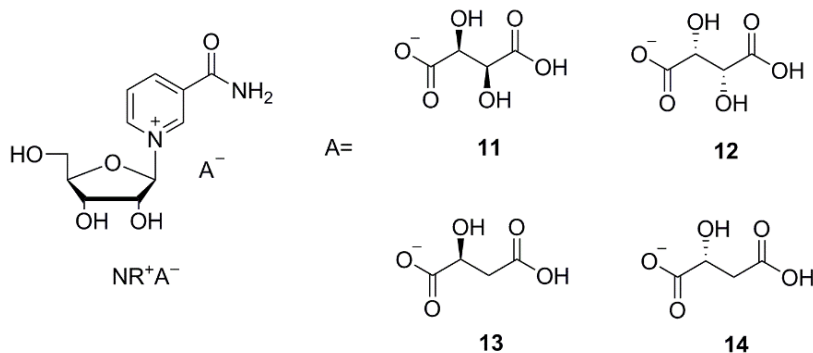
**Table 2.** Salt metathesis results with NR<sup>+</sup> acidic salts.

HA in Et <sub>3</sub> N·HA	NR <sup>+</sup> Br <sup>-</sup> (g)	H <sub>2</sub> O (mL)	MeOH (mL)	S/D*	Et <sub>3</sub> N·HA (mL)	NR·HA (g)	NR <sup>+</sup> Br <sup>-</sup> (g)	Yield %
Hydrogen citrate	0.92	-	2	S	1	-	**	0
Dihydrogen citrate	0.41	-	1	S	1	0.23		42
Hydrogen fumarate	0.58	-	1.5	S	1	-	**	0
Hydrogen maleate	0.58	-	1.5	S	1	-	0.13	0
D-Hydrogen malate	5.80	-	10	S	10	4.01		60
L-Hydrogen malate	5.80	-	10	S	10	4.15		62
DL-Hydrogen malate	5.80	-	10	S	10	4.52		67
Hydrogen malonate	0.60	-	1	S	1	-	0.07	0
H-mercaptosuccinate	0.58	-	1.5	S	1	-	**	0
Hydrogen ketoglutarate	0.58	-	1.5	S	1	-	**	0
Hydrogen oxalacetate	0.60	-	1	S	1	-	**	0
Hydrogen oxalate	0.62	-	1	S	1	-	0.15	0
Hydrogen succinate	0.58	-	1	S	1	-	**	0
D-Hydrogen tartrate	5.80	-	10	S	10	4.90		70
L-Hydrogen tartrate	5.80	3.5	10	D	10	6.62		95
DL-Hydrogen tartrate	5.80	3.5	10	D	10	6.31		90
meso-Hydrogen tartrate	0.57	-	1	S	1	0.44		62
Hydrogen tartronate	0.60	-	1	S	1	-	**	0

\* S = suspended, D = dissolved. \*\* The product was not dried and therefore the yield not determined.

The new crystalline salts, which are the acidic NR<sup>+</sup> salts of tartaric and malic acid (NR D-hydrogen tartrate **11**, NR L-hydrogen tartrate **12**, NR L-hydrogen tartrate **13**, and NR D-hydrogen tartrate **14**, shown in Figure 2) were isolated by using the above-described method not requiring elaborate crystallization experiments. These were formed immediately from salt metathesis with NR<sup>+</sup> bromide and were isolated with yields and purity

ranging from good to excellent. Furthermore, we determined that the residual bromide content was quite low (Table 3). Other bases such as tributylamine or tetrabutylammonium hydroxide can be used instead of Et<sub>3</sub>N, as reported in examples 10b, 10c, and 12b in the SI.



**Figure 2.** Structural formulas of the crystalline NR<sup>+</sup> derivatives: nicotinamide-β-D-ribose D-hydrogen tartrate (**11**), nicotinamide-β-D-ribose L-hydrogen tartrate (**12**), nicotinamide-β-D-ribose L-hydrogen malate (**13**), nicotinamide-β-D-ribose D-hydrogen malate (**14**).

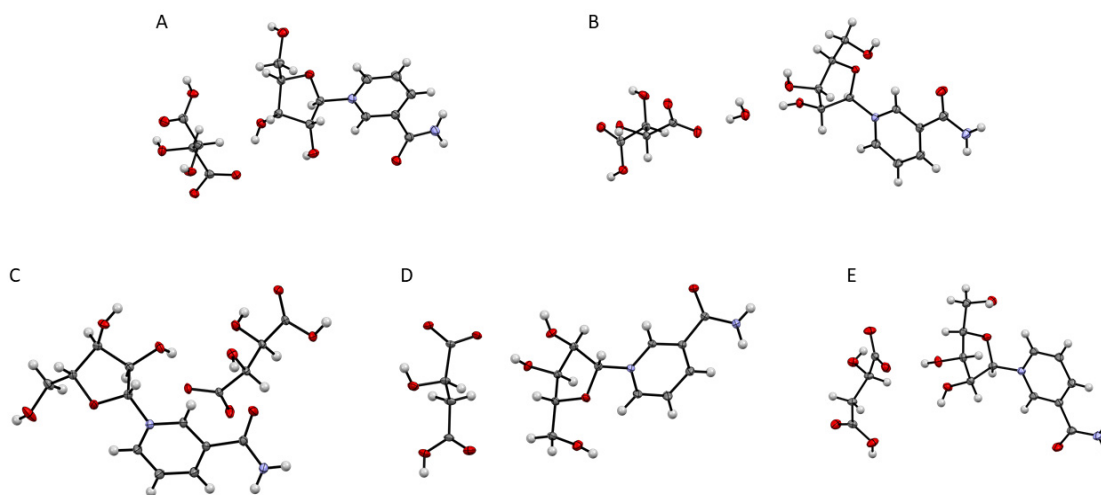
**Table 3.** Purity and residual bromide of crystalline NR<sup>+</sup> hydrogen malates and tartrates.

NR <sup>+</sup> Salt	Purity (NMR)	Residual Br (IC)
D-Hydrogen tartrate <b>11</b>	>97%	0.3%
L-Hydrogen tartrate <b>12</b>	>97%	0.2%
DL-Hydrogen tartrate <b>11</b> + <b>12</b>	>97%	0.1%
L-Hydrogen malate <b>13</b>	>97%	0.1%
D-Hydrogen malate <b>14</b>	>97%	0.9%
DL-Hydrogen malate <b>13</b> + <b>14</b>	>96%	2.3%

### 3.3. Single Crystal Growth of Newly Synthesized NR<sup>+</sup> Salts

Several re-crystallization attempts, which differed by method (vapor diffusion, controlled cooling, and under oil crystallization) and solvent type were set up for **11** through **14**.

After one week, single crystals of an anhydrate and hydrated derivative of **11** (**11a**, **11b**), and **12** were obtained. Rather rapid cooling delivered single crystals of **13** and **14** within half an hour, as well as two double salt derivatives: dinicotinamide-β-D-ribose L-hydrogen tartrate-D-hydrogen tartrate and dinicotinamide-β-D-ribose L-hydrogen malate-D-hydrogen malate which were crystallized via thermal crystallization. The crystalline nature was verified by powder X-ray diffractograms and single crystal structure investigations as shown in Figure 3 (additional data in Supporting Information). Interestingly, NR<sup>+</sup> *meso*-hydrogen tartrate was not crystalline.



**Figure 3.** Displacement ellipsoid representations at 50% probability of: **11a** (A) obtained by vapor diffusion; **11b** (B) and **12** (C) obtained by controlled cooling; **13** (D) and **14** (E) obtained by thermal crystallization and addition of an anti-solvent.

Single crystals of **11a** were obtained by vapor diffusion at room temperature from a saturated solution in methanol (MeOH), against a reservoir of tetrahydrofuran (THF). The single crystal X-ray diffraction data is summarized in Table S4, Supplementary Materials. **11a** crystallized in the monoclinic space group,  $P2_1$ . The asymmetric unit consists of one molecule of **11**, with two formula units per unit cell. The ribose sugar is in the C2' endo, twisted conformation. The absolute configuration of the enantiomerically pure molecule was confirmed by the Flack parameter (0.03(7)) and by the expected stereochemistry.

Monohydrated single crystals of **11b** were obtained by way of controlled cooling of a saturated solution in MeOH with 20% water at room temperature to 4 °C. Via this method, **11b** crystallized in the chiral, orthorhombic space group,  $P2_12_12_1$ . The asymmetric unit consist of **11** and a water molecule, which most likely originated from the non-dried methanol or from the humidity in the air. There are four formula units in one cell. The ribose sugar of **11b** (monohydrated) is in a C3' endo envelope conformation. The absolute configuration of the enantiomerically pure molecule was confirmed by the Flack parameter (0.02(5)) and its comparison to the expected stereochemistry. **11** was also characterized by powder X-ray diffraction. The measured powder pattern is shown in Figure S2A, Supplementary Materials. The powder pattern looks similar to the calculated powder pattern, simulated from single crystal data of the monohydrate (Figure S2C, Supplementary Materials), and less similar to the simulated pattern of the anhydrous crystal (Figure S2B, Supplementary Materials). This comparison indicates that the bulk compound exists as a monohydrate.

Single crystals of **12** were obtained by way of controlled cooling of a saturated solution of **12** dissolved in a 4:1 ratio of MeOH and water. The crystallographic data is summarized in Table S4, Supplementary Materials. **12** crystallized in the monoclinic space group  $P2_1$ . There are two formula units per unit cell and one molecule in the asymmetric unit. The ribose sugar is in a C2' endo envelope conformation. **12** was also characterized by powder X-ray diffraction. The measured powder pattern is shown in Figure S3A, Supplementary Materials. The powder pattern looks similar to the calculated powder pattern, simulated from single crystal data (Figure S3B, Supplementary Materials).

**13** crystallized in the monoclinic space group,  $P2_1$ . The asymmetric unit consists of one molecule of **13**, where the carboxylic acid of the first carbon is deprotonated. The unit cell holds two asymmetric units of molecule **13**. The ribose sugar is in a C3' endo envelope conformation. The absolute configuration of the enantiomerically pure molecule was confirmed by the Flack Parameter (0.03(14)) and by the expected stereochemistry. **13** was characterized by powder X-ray diffraction. The measured powder pattern is shown in Figure S4A, Supplementary Materials. The powder pattern is similar to the calculated

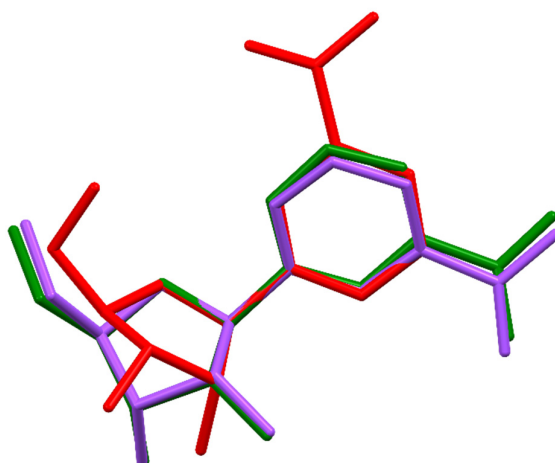
powder pattern, simulated from the single crystal data (Figure S4B, Supplementary Materials).

**14** crystallized in the chiral, orthorhombic, space group  $P2_12_12_1$ . The asymmetric unit contains only **14**, where the carboxylic acid attached to the first carbon is deprotonated, and there are four formula units per unit cell. The ribose sugar has a C3' endo envelope conformation. The absolute configuration of the enantiomerically pure molecule was confirmed by the Flack parameter (0.01(7)) and the expected stereochemistry. The powder pattern of **14** was simulated using the single crystal data. The result is shown in Figure S5, Supplementary Materials.

By comparison of **11–14**, it is evident that the anion type, and the stereochemistry of the anion is decisive for the overall structure. The space groups, the sugar pucker [66] conformations of **11–14** and a bromide and chloride salt from a previous work [34] as well as the  $\chi(O4-C1-N1-C6)$  torsion angles) are given in Table 4. The two anhydrous hydrogen tartrate diastereomers crystallized both into the space group  $P2_1$ , but the sugar of the D-hydrogen tartrate isomer has a twisted conformation, whereas L-hydrogen tartrate is in the C2'-endo envelope conformation. Alternatively, the hydrogen malate diastereomers did not crystallize in the same space groups. The L-isomer crystallized into the space group  $P2_1$  like L-hydrogen tartrate, but the D-hydrogen malate salt crystallized in the space group  $P2_12_12_1$ . Both malate isomers have riboside sugars in the 3' endo conformation. The L-hydrogen malate salt resembles the structures of the bromide and chloride anions of the nicotinamide riboside, as they crystallized into the same space groups with a 3' endo envelope conformation of sugars. The overlay of three representative structures (**11a**, **11b**, and **12**) are shown in Figure 4. The overlays were calculated by minimizing the distances between the atoms O4, C1, and N1 respectively. Apart from the 2'-endo versus 3'-endo differences, structure **11b** stood out, since it is the only structure with a positive  $\chi$  torsion angle of 10.9(2)° corresponding to a *syn* nucleoside confirmation. All the other structures have a negative  $\chi$  angle (between −136.1(1)° and −164.1(2)°) corresponding to an *anti* nucleoside confirmation.

**Table 4.** Sugar conformation of different NR<sup>+</sup> derivatives.

Compound	Space Group	Conformation	$\chi(O4-C1-N1-C6)$ [°]	Ref.
Nicotinamide- $\beta$ -D-ribose D-Hydrogen tartrate anhydrate ( <b>11a</b> )	$P2_1$	2'-endo, Twisted (in-between C1'-exo and C2'-endo)	−157.0(2)	This work
Nicotinamide- $\beta$ -D-ribose D-Hydrogen tartrate hydrate ( <b>11b</b> )	$P2_12_12_1$	3'-endo, Envelope	10.9(2)	This work
Nicotinamide- $\beta$ -D-ribose L-Hydrogen tartrate ( <b>12</b> )	$P2_1$	2'-endo, Envelope	−158.10(9)	This work
Nicotinamide- $\beta$ -D-ribose L-Hydrogen malate ( <b>13</b> )	$P2_1$	3'-endo, Envelope	−154.35(7)	This work
Nicotinamide- $\beta$ -D-ribose D-Hydrogen malate ( <b>14</b> )	$P2_12_12_1$	3'-endo, Envelope	−164.1(2)	This work
Nicotinamide- $\beta$ -D-ribose bromide	$P2_12_12_1$	3'-endo, Envelope	−137.1(2)	[34]
Nicotinamide- $\beta$ -D-ribose chloride	$P2_12_12_1$	3'-endo, Envelope	−136.1(1)	[34]



**Figure 4.** Overlay of the nicotinamide- $\beta$ -D-ribose cations of **11a**, **11b**, and **12**. The structures were overlaid on atoms O4, C1, and N1 with the help of the program Mercury.[64]

Additionally, the hydrogen bonding found differs in each structure. An attempt was made to simulate the PXRD of the L-hydrogen malate **13** by removal of the hydroxyl group from C14 of the D-hydrogen tartrate **11**, but this simulated pattern was very different from the PXRD pattern of **13**. This might suggest that the presence of one less hydrogen bond donor/acceptor on the anion is enough to change the orientation of the salt and the space group.

In summary, **11a**, **12**, and **13** all crystallized into the same space group, each with a different conformation of the riboside. **11b**, **14**, and the previously reported bromide and chloride salts [34] all crystallized into the same space group with the same sugar pucker conformation. However, the hydrogen bonding differs in each structure. Removal of an alcohol oxygen atom of D-hydrogen tartrate to yield L-hydrogen malate or of L-hydrogen tartrate to yield D-hydrogen malate respectively could in theory yield isostructural structures of the corresponding salt pairs, which is not the case. This suggests that the presence of one less hydrogen bond donor/acceptor on the anion is enough to change the orientation of the salt and the space group. In the absence of DFT studies, a quantitative explanation is not possible. Additionally, we observed that the double salts did not co-crystallize, rather they crystallized as the L- and D-enantiomers, separately [data not shown].

### 3.4. Properties of the New Crystalline NR<sup>+</sup> Salts

The solubility of the new NR<sup>+</sup> salts together with chloride and bromide NR<sup>+</sup> salts was tested. The solubility in water is comparable, however the new NR<sup>+</sup> salts were far less soluble in methanol (Table S3, Supplementary Materials). The low solubility in methanol is convenient since it allows for the synthesis of the new salts by salt metathesis from the bromide.

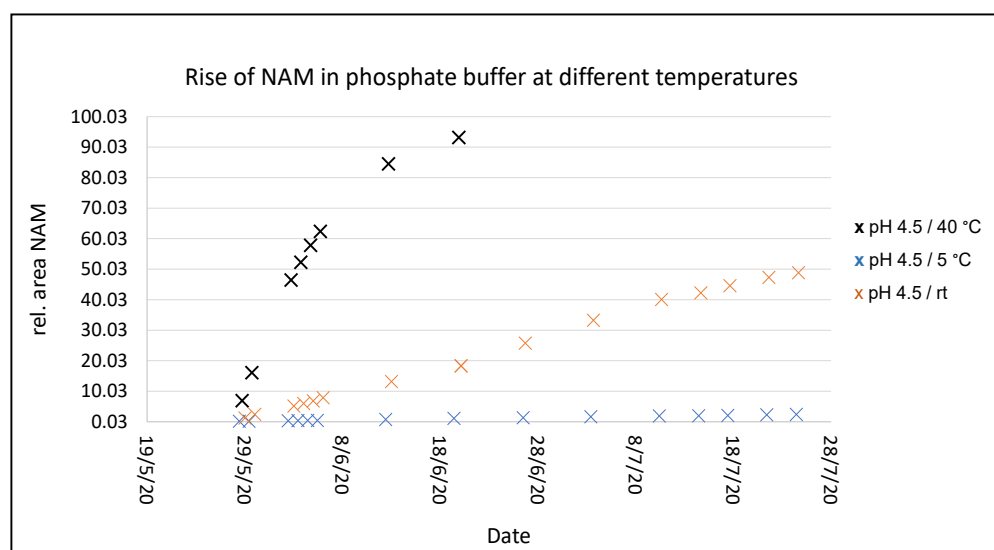
The stability of NR<sup>+</sup> hydrogen tartrate, hydrogen malate, chloride and bromide was tested in phosphate buffer at various acidic and neutral pHs (pH 2.5, pH 3.5, pH 4.5, pH 7.0, 0.75% hydrochloric acid), and at different temperatures (5 °C, RT, 40 °C) (data shown in Supplementary Materials).

The rate of degradation is dependent on temperature. At a given temperature, degradation to NAM occurs at the same rate regardless of NR<sup>+</sup> salt and pH. Comparing the different salts (different anions), no difference in stability could be found in solution. A slightly higher degradation rate under neutral (pH 7.0) conditions was found for the first few days, especially in the cases of NR<sup>+</sup> chloride and bromide. NR<sup>+</sup> hydrogen tartrate and hydrogen malate seem to be more stable at neutral pH, probably because they are slightly

acidic and can compensate for the negative effects of the surrounding solvent, being self-buffering.

After 3 weeks at 40 °C in solution, NR<sup>+</sup> is almost completely degraded to NAM. A slight flattening of the curve can be observed at higher NAM values. At RT, the degradation appears to be much slower: after 3 weeks only about 20% NAM is formed, compared to about 90% at 40 °C. At 5 °C after 3 weeks, just 1% NAM has formed, while when stored at pH 7.0 and a halogen as counter ion approximately 1.4% NAM formed. It can be concluded that the temperature has a decisive influence on the stability of the product in solution, while the pH has little impact.

The graph from Figure 5 shows the degradation rate of NR L-hydrogen malate into NAM at pH 4.5. A similar pH is obtained after dissolving the salt in water that, due to its slightly acidic character, brings the pH to this value. As explained, the pH has an insignificant effect on the degradation rate, while the temperature strongly influences it. The data was collected at 40 °C, 5 °C, and room temperature over several weeks, showing a much faster degradation for the higher temperature, while at low temperature it remains very stable. The rest of the salts behave similarly (individual data shown more in detail in the Supporting Information).

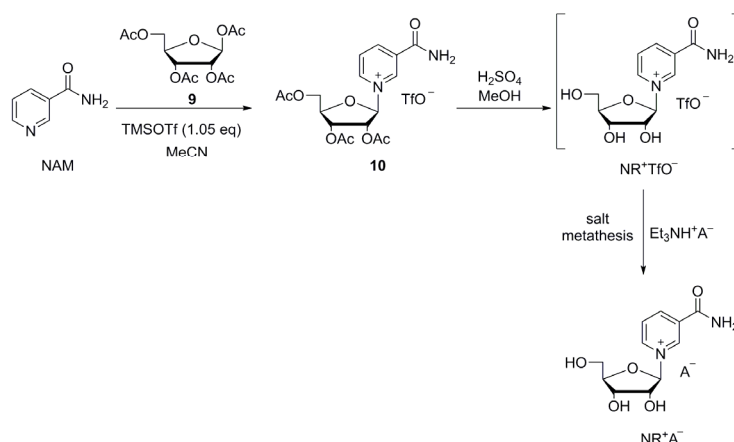


**Figure 5.** Degradation rate of NR<sup>+</sup> L-hydrogen malate to NAM as peak area measurement over time at pH 4.5 at different temperatures.

### 3.5. Improved Synthetic Approach via the Triflate NR<sup>+</sup>

Thanks to a thorough screening, we were able to identify new crystalline salts of NR<sup>+</sup>, which were initially synthesized via salt metathesis from NR<sup>+</sup> bromide. While this procedure is high yielding, manufacturing large amounts of NR<sup>+</sup> bromide would be too expensive for industrial production, and so an alternative synthetic route was explored. This involves deacetylation of NR<sup>+</sup>-triacetate triflate, followed by pH adjustment and salt metathesis with triethylammonium salts (Scheme 4).

NR<sup>+</sup>-triacetate triflate is formed directly from ribose tetraacetate and NAM activated in situ with TMSOTf, with an almost quantitative turnover. Since no excess reagent is required, no by-products must be separated, and no special vacuum pumps are needed. The reaction is easy to carry out without special equipment and proceeds gently. The stable NR<sup>+</sup>-triacetate triflate can be processed and deacetylated immediately, and the final product crystallizes directly from the reaction solution upon salt metathesis. All three stages can be carried out in one go, making it a convenient one-pot process.



**Scheme 4.** Improved synthetic route via NR triflate.

NR<sup>+</sup>-triacetate iodide was also synthesized, as reported in examples 17 and 18 in the SI. However, the reaction required a higher temperature to proceed (40–45 °C) and the conversion did not go to completion. For this reason, the synthesis of the triflate derivative is preferred.

By comparison, the 1-chloro-2,3,5-triacetyl-D-ribofuranose must be prepared separately using HCl gas or acetyl chloride. This is difficult to scale up because the chlorosugar is unstable under the reaction conditions. For full conversion, excess HCl is necessary. Removal of excess HCl requires special, corrosion-resistant vacuum pumps and increased temperatures that are unfavorable for the glycosylation.

According to Tanimori et al. [49] glycosylation of NAM takes place on activation of ribose tetraacetate **10** by an excess of TMSOTf (Scheme 4). We found, however, just over one equivalent is sufficient for almost complete conversion. The avoidance of such a large excess of the expensive, hazardous, and air-sensitive TMSOTf is a great economical advantage compared to previously described methodologies. The triacetate was not isolated by the authors, but immediately deacetylated in situ after the addition of methanol. The deprotected NR<sup>+</sup> triflate was described by the authors as a crystalline substance, but no evidence supporting this statement was reported. However, the triflate obtained from our experiments proved to be non-crystalline. Surprisingly, ammonia is used in most procedures to remove the acyl protecting groups of the NR<sup>+</sup> salt [42,43,45,46,50,54,55], although an alkaline environment leads to considerable decomposition. We also proved experimentally that the resinous NR<sup>+</sup>-triacetate triflate **10** may be deacetylated with ammonia in methanol. However, we realized that deacetylation with mineral acids is a cleaner procedure leading to the formation of less impurities. We found that deacetylation is also possible by employing triethylamine, obtaining higher yields (Scheme 4).

Additionally, we attempted deacetylation with HBr and we observed that the bromide crystallized, but its yield was unexpectedly low. When we used HCl the yield of the chloride resulted in being even lower. This shows that both halogenides are not ideal to isolate the NR<sup>+</sup> out of the metathesis mixture. The difference in yield clearly highlights the benefit of the new NR<sup>+</sup> salts described in this work for economic synthesis of NR<sup>+</sup> salts. We would therefore recommend using sulfuric acid for deacetylation, because it avoids the disturbing crystallization of undesired salts such as NR<sup>+</sup> bromide. The overall yields (from the three steps of glycosylation, deacetylation, and salt metathesis) obtained with the various deacetylation methods are reported in Table 5.

**Table 5.** Yields of the newly obtained NR salts with various methodologies.

Example (SI)	Deacetylation	Neutralization	Salt for SM	Product	Yield %
15a	H <sub>2</sub> SO <sub>4</sub>	Et <sub>3</sub> N	Et <sub>3</sub> N L-H-Tartrate	NR <sup>+</sup> L-H-Tartrate	54
15b	HBr	-	-	NR <sup>+</sup> Bromide	25
15b	HBr	Et <sub>3</sub> N	Et <sub>3</sub> N L-H-Tartrate	NR <sup>+</sup> L-H-Tartrate	53
15c	HCl	-	-	NR <sup>+</sup> Chloride	2
15c	HCl	Et <sub>3</sub> N	Et <sub>3</sub> N L-H-Tartrate	NR <sup>+</sup> L-H-Tartrate	60
15d	Et <sub>3</sub> N	-	Et <sub>3</sub> N L-H-Tartrate	NR <sup>+</sup> L-H-Tartrate	63
16a	H <sub>2</sub> SO <sub>4</sub>	Et <sub>3</sub> N	Et <sub>3</sub> N L-H-Malate	NR <sup>+</sup> L-H-Malate	37
16b	HBr	Bu <sub>3</sub> N	Et <sub>3</sub> N L-H-Malate	NR <sup>+</sup> L-H-Malate	33
16c	HCl	Et <sub>3</sub> N	Et <sub>3</sub> N L-H-Malate	NR <sup>+</sup> L-H-Malate	43
16d	Et <sub>3</sub> N	-	Et <sub>3</sub> N L-H-Malate	NR <sup>+</sup> L-H-Malate	43

The improved synthetic procedure described above is extremely convenient because once the NR<sup>+</sup> cation is formed, it can be converted into a desired NR<sup>+</sup> salt simply by double conversion, provided that the salt is either crystalline or at least precipitable as an amorphous solid. To promote precipitation or crystallization of the NR<sup>+</sup> salt, a pH adjustment can be performed. With this newly described method, the desired NR<sup>+</sup> hydrogen tartrate or hydrogen malate salts precipitated from the reaction solution as the least soluble and the only crystalline phase. Due to the low solubility and high crystallization tendency of the new salts in methanol, the products obtained are already quite pure and only require one further recrystallization to be suitable for food additives.

#### 4. Conclusions

In conclusion, after a thorough screening, we discovered new pharmaceutically suitable NR<sup>+</sup> salts, specifically high-crystalline NR<sup>+</sup> hydrogen malate and NR<sup>+</sup> hydrogen tartrate salts with numerous favorable properties. These salts were initially synthesized via salt metathesis from NR<sup>+</sup> bromide. A fast re-crystallization step allowed us to obtain single crystals and elucidate their crystal structure. Once pharmaceutically suitable forms of NR<sup>+</sup> salts were identified, the synthetic procedure was greatly improved to a high yielding one-pot procedure, not requiring specific and expensive apparatus. The improved yields and the ease of production are suitable for large-scale industrial manufacturing compatible with distribution in the food supplement global market.

The newly reported compounds are salts of well-known anions, which are metabolites produced in vivo and also present in the market as food supplements. The new NR<sup>+</sup> salts can therefore be safely administered orally as food supplements. In fact, NR<sup>+</sup> is fully solvated in water and its reactivity and physiology does not depend on its counter ion, as long as this is benign.

#### 5. Patents

Some of the experimental results and procedures presented in this manuscript are collected in the patent application number WO 2021/013795 A2.

**Supplementary Materials:** Section S1: Preparation of neutral salts. Section S2: Preparation of acidic salts. Section S3: Solubility of NR<sup>+</sup> crystalline salts. Section S4: Single crystal growth and structural determination of nicotinamide riboside derivatives by X-ray diffraction. Section S5: Stability studies of NR<sup>+</sup> salts. Figure S1: Photos of the grown crystals of **11a** (anhydrate of **11**) (A), **11b** (monohydrate of **11**) (B), **12** (C), **13** (D) and **14** (E); Figure S2: X-ray powder pattern of **11** (A). X-ray powder pattern of **11a** (anhydrous) simulated from single crystal data (B). X-ray powder pattern of **11b** (monohydrate) simulated from single crystal data (C). Figure S3: X-ray powder pattern of **12** (A). X-ray powder pattern of **12** simulated from single crystal data (B); Figure S4: X-ray powder pattern of **13** (A). X-ray powder pattern of **13** simulated from single crystal data (B); Figure S5: X-ray powder pattern of **14** (A). X-ray powder pattern of **14** simulated from single crystal data (B); Figure S6: NAM peak area measurement over time at RT at various pH for NR<sup>+</sup>-L-hydrogen malate (A), NR<sup>+</sup>-DL-hydrogen



tartrate (**B**), NR<sup>+</sup> chloride (**C**), NR<sup>+</sup> bromide (**D**); Comparison of the different NR<sup>+</sup> Salts at RT in HCl (**E**); Figure S7: NAM peak area measurement over time at 5 °C at various pH for NR<sup>+</sup>-L-hydrogen malate (**A**), NR<sup>+</sup>-DL-hydrogen tartrate (**B**), NR<sup>+</sup>-chloride (**D**), NR<sup>+</sup>-bromide (**E**); Comparison of the different NR<sup>+</sup> Salts at 5 °C in HCl (**F**); Figure S8: NAM peak area measurement over time at 40 °C at various pH for NR<sup>+</sup>-L-hydrogen malate (**A**), NR<sup>+</sup>-DL-hydrogen tartrate (**B**), NR<sup>+</sup>-chloride (**D**), NR<sup>+</sup>-bromide (**E**); Comparison of the different NR<sup>+</sup> Salts at 40 °C in HCl (**F**); Table S1: Carboxylic acids used to prepare the Et<sub>3</sub>N·A solutions; Table S2: Dicarboxylates used to prepare the Et<sub>3</sub>N·HA solutions; Table S3: Solubilities (in mL solvent per g of solute) of the stereoisomeric crystalline NR<sup>+</sup> salts and the halogenides in methanol and in aqueous solutions; Table S4: Summary of Crystal Data and Structure Refinement of the Salts **11a**, **11b**, **12**, **13**, and **124**.

**Author Contributions:** The following statements should be used “Conceptualization, G.S., R.H., B.S., and U.S.; methodology, G.S., R.H., and B.S.; validation, G.S., R.H., B.S., and J.P.; formal analysis, G.S., R.H., B.S., and J.P.; investigation, G.S., R.H., B.S., and J.P.; resources, G.S., R.H., B.S., and U.S.; data curation, G.S., R.H., and B.S.; writing—original draft preparation, G.S., J.P., and L.P.; writing—review and editing, L.P., G.S., R.H., B.S., J.P., A.H-B, and U.S.; visualization, L.P., G.S., R.H., B.S., and J.P.; supervision, B.S. and U.S.; project administration, A.H-B., B.S., and U.S.; funding acquisition, B.S. and U.S. All authors have read and agreed to the published version of the manuscript.

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**Sample Availability:** Samples of the compounds are not available from the authors.

## References

- Chini, C.C.; Tarragó, M.G.; Chini, E.N. NAD and the aging process: Role in life, death and everything in between. *Mol. Cell. Endocrinol.* **2017**, *455*, 62–74, doi:10.1016/j.mce.2016.11.003.
- Verdin, E. NAD<sup>+</sup> in aging, metabolism, and neurodegeneration. *Sci.* **2015**, *350*, 1208–1213, doi:10.1126/science.aac4854.
- Hirschey, M.D. Old Enzymes, New Tricks: Sirtuins Are NAD<sup>+</sup>-Dependent De-acylases. *Cell Metab.* **2011**, *14*, 718–719, doi:10.1016/j.cmet.2011.10.006.
- Fang, E.F.; Lautrup, S.; Hou, Y.; Demarest, T.G.; Croteau, D.L.; Mattson, M.P.; Bohr, V.A. NAD<sup>+</sup> in Aging: Molecular Mechanisms and Translational Implications. *Trends Mol. Med.* **2017**, *23*, 899–916, doi:10.1016/j.molmed.2017.08.001.
- Ziegler, M.; Niere, M. NAD<sup>+</sup> surfaces again. *Biochem. J.* **2004**, *382*, E5–6, doi:10.1042/bj20041217.
- A Sauve, A.; Youn, D.Y. Sirtuins: NAD<sup>+</sup>-dependent deacetylase mechanism and regulation. *Curr. Opin. Chem. Biol.* **2012**, *16*, 535–543, doi:10.1016/j.cbpa.2012.10.003.
- Imai, S.-I.; Guarente, L. NAD<sup>+</sup> and sirtuins in aging and disease. *Trends Cell Biol.* **2014**, *24*, 464–471, doi:10.1016/j.tcb.2014.04.002.
- Sassone-Corsi, P. Minireview: NAD<sup>+</sup>, a Circadian Metabolite with an Epigenetic Twist. *Endocrinol.* **2012**, *153*, 1–5, doi:10.1210/en.2011-1535.
- Braid, N.; Berg, J.; Clement, J.; Khorshidi, F.; Poljak, A.; Jayasena, T.; Grant, R.; Sachdev, P. Role of Nicotinamide Adenine Dinucleotide and Related Precursors as Therapeutic Targets for Age-Related Degenerative Diseases: Rationale, Biochemistry, Pharmacokinetics, and Outcomes. *Antioxidants Redox Signal.* **2019**, *30*, 251–294, doi:10.1089/ars.2017.7269.
- Denu, J.M. Vitamins and aging: pathways to NAD<sup>+</sup> synthesis. *Cell* **2007**, *129*, 453–4, doi:10.1016/j.cell.2007.04.023.
- Hosseini, L.; Vafaee, M.S.; Mahmoudi, J.; Badalzadeh, R. Nicotinamide adenine dinucleotide emerges as a therapeutic target in aging and ischemic conditions. *Biogerontology* **2019**, *20*, 381–395, doi:10.1007/s10522-019-09805-6.
- Zheng, C.; Han, J.; Xia, W.; Shi, S.; Liu, J.; Ying, W. NAD<sup>+</sup> administration decreases ischemic brain damage partially by blocking autophagy in a mouse model of brain ischemia. *Neurosci. Lett.* **2012**, *512*, 67–71, doi:10.1016/j.neulet.2012.01.007.
- Cattelan, A.; Ceolotto, G.; Bova, S.; Albiero, M.; Kuppasamy, M.; De Martin, S.; Semplicini, A.; Fadini, G.P.; de Kreutzenberg, S.V.; Avogaro, A. NAD<sup>+</sup>-dependent SIRT1 deactivation has a key role on ischemia–reperfusion-induced apoptosis. *Vasc. Pharmacol.* **2015**, *70*, 35–44, doi:10.1016/j.vph.2015.02.004.
- Jokinen, R.; Pirnes-Karhu, S.; Pietiläinen, K.H.; Pirinen, E. Adipose tissue NAD<sup>+</sup>-homeostasis, sirtuins and poly(ADP-ribose) polymerases—important players in mitochondrial metabolism and metabolic health. *Redox Biol.* **2017**, *12*, 246–263, doi:10.1016/j.redox.2017.02.011.
- Nielsen, K.N.; Peics, J.; Ma, T.; Karavaeva, I.; Dall, M.; Chubanova, S.; Basse, A.L.; Dmytriyeva, O.; Treebak, J.T.; Gerhart-Hines, Z. NAMPT-mediated NAD biosynthesis is indispensable for adipose tissue plasticity and development of obesity. *Mol. Metab.* **2018**, *11*, 178–188, doi:10.1016/j.molmet.2018.02.014.

16. Yamaguchi, S.; Yoshino, J. Adipose tissue NAD<sup>+</sup>biology in obesity and insulin resistance: From mechanism to therapy. *BioEssays* **2017**, *39*, 1600227, doi:10.1002/bies.201600227.
17. Yan, L.-J.; Wu, J.; Jin, Z.; Zheng, H. Sources and implications of NADH/NAD<sup>+</sup> redox imbalance in diabetes and its complications. *Diabetes, Metab. Syndr. Obesity: Targets Ther.* **2016**, *9*, 145–153, doi:10.2147/dmso.s106087.
18. Berthiaume, J.M.; Kurdys, J.G.; Muntean, D.M.; Rosca, M.G. Mitochondrial NAD<sup>+</sup>/NADH Redox State and Diabetic Cardiomyopathy. *Antioxidants Redox Signal.* **2019**, *30*, 375–398, doi:10.1089/ars.2017.7415.
19. Elhassan, Y.S.; Philp, A.A.; Lavery, G.G. Targeting NAD<sup>+</sup> in Metabolic Disease: New Insights Into an Old Molecule. *J. Endocr. Soc.* **2017**, *1*, 816–835, doi:10.1210/js.2017-00092.
20. Lautrup, S.; Sinclair, D.A.; Mattson, M.P.; Fang, E.F. NAD<sup>+</sup> in Brain Aging and Neurodegenerative Disorders. *Cell Metab.* **2019**, *30*, 630–655, doi:10.1016/j.cmet.2019.09.001.
21. Figley, M.D.; DiAntonio, A. The SARM1 axon degeneration pathway: control of the NAD<sup>+</sup> metabolome regulates axon survival in health and disease. *Curr. Opin. Neurobiol.* **2020**, *63*, 59–66, doi:10.1016/j.conb.2020.02.012.
22. Yoshino, J.; Baur, J.A.; Imai, S.-I. NAD<sup>+</sup> Intermediates: The Biology and Therapeutic Potential of NMN and NR. *Cell Metab.* **2018**, *27*, 513–528, doi:10.1016/j.cmet.2017.11.002.
23. Mehmehl, M.; Jovanović, N.; Spitz, U. Nicotinamide Riboside—The Current State of Research and Therapeutic Uses. *Nutr.* **2020**, *12*, 1616, doi:10.3390/nu12061616.
24. Schöndorf, D.C.; Ivanyuk, D.; Baden, P.; Sanchez-Martinez, A.; De Cicco, S.; Yu, C.; Giunta, I.; Schwarz, L.K.; Di Napoli, G.; Panagiotakopoulou, V.; et al. The NAD<sup>+</sup> Precursor Nicotinamide Riboside Rescues Mitochondrial Defects and Neuronal Loss in iPSC and Fly Models of Parkinson's Disease. *Cell Rep.* **2018**, *23*, 2976–2988, doi:10.1016/j.celrep.2018.05.009.
25. Bieganski, P.; Brenner, C. Discoveries of Nicotinamide Riboside as a Nutrient and Conserved NRK Genes Establish a Preiss-Handler Independent Route to NAD<sup>+</sup> in Fungi and Humans. *Cell* **2004**, *117*, 495–502, doi:10.1016/s0092-8674(04)00416-7.
26. Bogan, K.L.; Brenner, C. Nicotinic Acid, Nicotinamide, and Nicotinamide Riboside: A Molecular Evaluation of NAD<sup>+</sup> Precursor Vitamins in Human Nutrition. *Annu. Rev. Nutr.* **2008**, *28*, 115–130, doi:10.1146/annurev.nutr.28.061807.155443.
27. Knip, M.; Douek, I.F.; Moore, W.P.T.; Gillmor, H.A.; McLean, A.E.M.; Bingley, P.J.; Gale, E.A.M. Safety of high-dose nicotinamide: a review. *Diabetol.* **2000**, *43*, 1337–1345, doi:10.1007/s001250051536.
28. Conze, D.B.; Crespo-Barreto, J.; Kruger, C.L. Safety assessment of nicotinamide riboside, a form of vitamin B3. *Hum. Exp. Toxicol.* **2016**, *35*, 1149–1160, doi:10.1177/0960327115626254.
29. Ishtiaq, Y.; Nkrumah-Elie, Y.; Idoine, R.; Roberts, M.; Shao, A. Application of the Frameworks of Intrinsic Capacity and the Hallmarks of Aging to Validate Nicotinamide Riboside as a Healthy Aging Supplement – A Meta-Analysis. *Curr. Dev. Nutr.* **2020**, *4*, 36, doi:10.1093/cdn/nzaa040\_036.
30. Fletcher, R.S.; Ratajczak, J.; Doig, C.L.; Oakey, L.A.; Callingham, R.; Xavier, G.D.S.; Garten, A.; Elhassan, Y.S.; Redpath, P.; Migaud, M.; et al. Nicotinamide riboside kinases display redundancy in mediating nicotinamide mononucleotide and nicotinamide riboside metabolism in skeletal muscle cells. *Mol. Metab.* **2017**, *6*, 819–832, doi:10.1016/j.molmet.2017.05.011.
31. Kulikova, V.; Shabalin, K.; Nerinovski, K.; Dölle, C.; Niere, M.; Yakimov, A.; Redpath, P.; Khodorkovskiy, M.; Migaud, M.E.; Ziegler, M.; et al. Generation, Release, and Uptake of the NAD Precursor Nicotinic Acid Riboside by Human Cells. *J. Biol. Chem.* **2015**, *290*, 27124–27137, doi:10.1074/jbc.m115.664458.
32. Zhang, H.; Ryu, D.; Wu, Y.; Gariani, K.; Wang, X.; Luan, P.; D'Amico, D.; Ropelle, E.R.; Lutolf, M.P.; Aebbersold, R.; et al. NAD<sup>+</sup> repletion improves mitochondrial and stem cell function and enhances life span in mice. *Sci.* **2016**, *352*, 1436–1443, doi:10.1126/science.aaf2693.
33. Makarov, M.V.; E Migaud, M. Syntheses and chemical properties of  $\beta$ -nicotinamide riboside and its analogues and derivatives. *Beilstein J. Org. Chem.* **2019**, *15*, 401–430, doi:10.3762/bjoc.15.36.
34. Alvarez, R.; Schabert, G.; Soydemir, A.; Wick, L.; Spitz, U.; Spingler, B. Nicotinamide Riboside Derivatives: Single Crystal Growth and Determination of X-ray Structures. *Cryst. Growth Des.* **2019**, *19*, 4019–4028, doi:10.1021/acs.cgd.9b00423.
35. Airhart, S.E.; Shireman, L.M.; Risler, L.J.; Anderson, G.D.; Gowda, G.A.N.; Raftery, D.; Tian, R.; Shen, D.D.; O'Brien, K.D. An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD<sup>+</sup> levels in healthy volunteers. *PLOS ONE* **2017**, *12*, e0186459, doi:10.1371/journal.pone.0186459.
36. Martens, C.R.; Denman, B.A.; Mazzo, M.R.; Armstrong, M.L.; Reisdorph, N.; McQueen, M.B.; Chonchol, M.; Seals, D.R. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD<sup>+</sup> in healthy middle-aged and older adults. *Nat. Commun.* **2018**, *9*, 1286, doi:10.1038/s41467-018-03421-7.
37. Cantó, C.; Houtkooper, R.H.; Pirinen, E.; Youn, D.Y.; Oosterveer, M.H.; Cen, Y.; Fernandez-Marcos, P.J.; Yamamoto, H.; Andreux, P.A.; Cettour-Rose, P.; et al. The NAD<sup>+</sup> Precursor Nicotinamide Riboside Enhances Oxidative Metabolism and Protects against High-Fat Diet-Induced Obesity. *Cell Metab.* **2012**, *15*, 838–847, doi:10.1016/j.cmet.2012.04.022.
38. Belenky, P.; Racette, F.G.; Bogan, K.L.; McClure, J.M.; Smith, J.S.; Brenner, C. Nicotinamide Riboside Promotes Sir2 Silencing and Extends Lifespan via Nrk and Urh1/Pnp1/Meu1 Pathways to NAD<sup>+</sup>. *Cell* **2007**, *129*, 473–484, doi:10.1016/j.cell.2007.03.024.
39. Tempel, W.; Rabeh, W.M.; Bogan, K.L.; Belenky, P.; Wójcik, M.; Seidle, H.F.; Nedyalkova, L.; Yang, T.; A Sauve, A.; Park, H.-W.; et al. Nicotinamide Riboside Kinase Structures Reveal New Pathways to NAD<sup>+</sup>. *PLoS Biol.* **2007**, *5*, e263, doi:10.1371/journal.pbio.0050263.
40. Dollerup, O.L.; Christensen, B.; Svart, M.; Schmidt, M.S.; Sulek, K.; Ringgaard, S.; Stødkilde-Jørgensen, H.; Møller, N.; Brenner, C.; Treebak, J.T.; et al. A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity, and lipid-mobilizing effects. *Am. J. Clin. Nutr.* **2018**, *108*, 343–353, doi:10.1093/ajcn/nqy132.

41. Trammell, S.A.J.; Schmidt, M.S.; Weidemann, B.J.; Redpath, P.; Jaksch, F.; Dellinger, R.W.; Philip, R.; Abel, E.D.; Migaud, M.E.; Brenner, C. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. *Nat. Commun.* **2016**, *7*, 12948, doi:10.1038/ncomms12948.
42. Haynes, L.J.; Todd, A.R. 66. Codehydrogenases. Part I. The synthesis of dihydronicotinamide-D-ribofuranoside [N-D-ribofuranosidyl-1 : 2(or 6)-dihydronicotinamide]. *J. Chem. Soc.* **1950**, 303–308, doi:10.1039/jr9500000303.
43. Haykes, L.J.; Hughes, N.A.; Kenner, G.W.; Todd, A. 734. Codehydrogenases. Part II. A synthesis of nicotinamide nucleotide. *J. Chem. Soc.* **1957**, 3727–3732, doi:10.1039/jr9570003727.
44. Mikhailopulo, I.A.; Pricota, T.I.; Timoshchuk, V.A.; Akhrem, A.A. Synthesis of Glycosides of Nicotinamide and Nicotinamide Mononucleotide. *Synth.* **1981**, 1981, 388–389, doi:10.1055/s-1981-29462.
45. Lee, J.; Churchill, H.; Choi, W.-B.; Lynch, J.E.; Roberts, F.E.; Volante, R.P.; Reider, P.J. A chemical synthesis of nicotinamide adenine dinucleotide (NAD<sup>+</sup>). *Chem. Commun.* **1999**, 729–730, doi:10.1039/a809930h.
46. Jarman, M.; Ross, W.C.J. 4-Substituted nicotinic acids and nicotinamides. Part II. The preparation of 4-methylnicotinamide riboside. *J. Chem. Soc. C* **1969**, 199–203, doi:10.1039/j39690000199.
47. Migaud, M.E.; Redpath, P.; Crossey, K.; Cunningham, R.; Erickson, A.; Nygaard, R.; Storjohann, A. Efficient and Scalable Syntheses of Nicotinoyl Ribosides and Reduced Nicotinoyl Ribosides, Modified Derivatives Thereof, Phosphorylated Analogs Thereof, Adenylyl Dinucleotide Conjugates Thereof, and Novel Crystalline Forms Thereof, 2018/089830 A1, 17 May 2018.
48. Migaud, M.E.; Redpath, P.; Crossey, K.; Cunningham, R.; Dellinger, R.; Rhonemus, T.; Venkataraman, S.; Nettles, B. B-Vitamin and Amino Acid Conjugates of Nicotinoyl Ribosides and Reduced Nicotinoyl Ribosides, Derivatives Thereof, and Methods of Preparation Thereof, 2017/161165 A1, 21 September 2017.
49. Tanimori, S.; Ohta, T.; Kirihata, M. An efficient chemical synthesis of nicotinamide riboside (NAR) and analogues. *Bioorganic Med. Chem. Lett.* **2002**, *12*, 1135–1137, doi:10.1016/s0960-894x(02)00125-7.
50. Franchetti, P.; Pasqualini, M.; Petrelli, R.; Ricciutelli, M.; Vita, P.; Cappellacci, L. Stereoselective synthesis of nicotinamide  $\beta$ -riboside and nucleoside analogs. *Bioorganic Med. Chem. Lett.* **2004**, *14*, 4655–4658, doi:10.1016/j.bmcl.2004.06.093.
51. Dellinger, R.; Migaud, M.E.; Redpath, P.; Rhonemus, T.; Cunningham, R. Nicotinic Acid Riboside or Nicotinamide Riboside Compositions, Reduced Derivatives Thereof, and the Use Thereof, 2016/149395 A1. 22 September 2016.
52. Szczepankiewicz, B.; Koppetsch, K.; Perni, R.B. Preparation and Use of Crystalline Beta-D-Nicotinamide Riboside. 2015/186068 A1. WO Patent. 10 December 2015.
53. Fouquerel, E.; Goellner, E.M.; Yu, Z.; Gagné, J.-P.; De Moura, M.B.; Feinstein, T.; Wheeler, D.; Redpath, P.; Li, J.; Romero, G.; et al. ARTD1/PARP1 Negatively Regulates Glycolysis by Inhibiting Hexokinase 1 Independent of NAD<sup>+</sup> Depletion. *Cell Rep.* **2014**, *8*, 1819–1831, doi:10.1016/j.celrep.2014.08.036.
54. Yang, T.; Chan, N.Y.-K.; Sauve, A.A. Syntheses of Nicotinamide Riboside and Derivatives: Effective Agents for Increasing Nicotinamide Adenine Dinucleotide Concentrations in Mammalian Cells. *J. Med. Chem.* **2007**, *50*, 6458–6461, doi:10.1021/jm701001c.
55. Zhang, N.; Sauve, A.A. Synthesis of  $\beta$ -Nicotinamide Riboside Using an Efficient Two-Step Methodology. *Current Protocols in Nucleic Acid Chemistry* **2017**, *71*, 14.14.1–14.14.9, doi:10.1002/cpnc.43.
56. Sauve, A.A.; Yang, T.; Nicotinoyl Riboside Compositions and Methods of Use. 8,106,184 B2. 31 January 2012.
57. Felczak, K.Z. Synthetic Methods for the Preparation of Nicotinamide Riboside and Related Compounds. 2017/218580 A1. 21 December 2017.
58. Spingler, B.; Schnidrig, S.; Todorova, T.; Wild, F. Some thoughts about the single crystal growth of small molecules. *CrystEngComm* **2012**, *14*, 751–757, doi:10.1039/c1ce05624g.
59. Babor, M.; Nievergelt, P.P.; Čejka, J.; Zvoníček, V.; Spingler, B. Microbatch under-oil salt screening of organic cations: single-crystal growth of active pharmaceutical ingredients. *IUCr* **2019**, *6*, 145–151, doi:10.1107/s2052252518017876.
60. CrysAlisPro Software System; Rigaku Oxford Diffraction, Rigaku Corporation, 2019.
61. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Cryst. Sect. C Struct. Chem.* **2015**, *71*, 3–8, doi:10.1107/S2053229614024218.
62. Sheldrick, G.M. SHELXT—Integrated space-group and crystal-structure determination. *Acta Cryst. Sect. A Found. Adv.* **2015**, *71*, 3–8, doi:10.1107/s2053273314026370.
63. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **2009**, *42*, 339–341, doi:10.1107/s0021889808042726.
64. Macrae, C.F.; Sovago, I.; Cottrell, S.J.; Galek, P.T.A.; McCabe, P.; Pidcock, E.; Platings, M.; Shields, G.P.; Stevens, J.S.; Towler, M.; et al. Mercury 4.0: from visualization to analysis, design and prediction. *J. Appl. Crystallogr.* **2020**, *53*, 226–235, doi:10.1107/s1600576719014092.
65. Spek, A.L. Structure validation in chemical crystallography. *Acta Crystallogr. Sect. D Biol. Crystallogr.* **2009**, *65*, 148–155, doi:10.1107/s090744490804362x.
66. Egli, M.; Saenger, W. *Principles of Nucleic Acid Structure*; Springer: Berlin/Heidelberg, Germany, 1983.

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New crystalline salts of nicotinamide riboside as food additives

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## Supporting Information

- Section S1: Preparation of neutral salts
- Section S2: Preparation of acidic salts
- Section S3: Solubility of NR<sup>+</sup> crystalline salts
- Section S4: Single Crystal Growth and Structural Determination of Nicotinamide riboside derivatives by X-Ray Diffraction
- Section S5: Stability studies of NR<sup>+</sup> salts

## Section S1: Preparation of neutral salts

### Preparation of solutions of Et<sub>3</sub>N·(di)-Carboxylate (Et<sub>3</sub>N·A), general procedure

The carboxylic acid was suspended (S) or dissolved (D) in methanol (MeOH) while stirring at RT. The solution was cooled in an ice bath and a multi-equivalent amount of triethylamine (Et<sub>3</sub>N) sufficient for complete neutralisation was added, after which a slight temperature increase was observed. The pH of the colourless to yellowish solutions was about 8. The exceptions are the glucuronate solution with pH around 7, the fumarate and succinate solutions with pH around 6. With the general method described above, x mL of a y molar Et<sub>3</sub>N-carboxylate solution (Et<sub>3</sub>N·A) were obtained and used directly in the next step without further purification. The data for the carboxylic acid tested are reported in Table S1.

Table S1: Carboxylic acids used to prepare the Et<sub>3</sub>N·A solutions.

Carboxylic acid	Acid Amount	MeOH (mL)	S / D	Et <sub>3</sub> N (mL)	x (mL)	y (M)
L-Ascorbic	4.50 g	22.5	S	3.64	27.5	0.93
Benzenesulfonic	4.38 g	10.0	D	3.64	15.5	1.68
Citric	5.52 g*	55.0**	D	12.00	73.00	0.36
Formic	1.40 mL	10.0	D	5.00	15.00	2.40
Fumaric	3.02 g	10.0	S	7.28	17.50	1.49
D-Glucuronic	5.10 g	15.0	S	3.60	19.50	1.32
L-Lactic	2.34 g	10.0	D	3.64	15.00	1.73
L-Malic	3.50 g	10.0	D	7.30	18.00	1.45
Maleic	3.02 g	10.0	D	7.27	18.50	1.40
Malonic	2.70 g	10.0	D	7.27	18.00	1.45
Methanesulfonic	1.70 mL	10.0	S	3.64	14.00	1.86
Salicylic	3.60 g	10.0	D	3.64	16.00	1.63
Sorbic	2.94 g	10.0	S	3.64	15.50	1.68
Succinic	3.07 g	10.0	S	7.28	18.00	1.44
L-Tartaric	3.90 g	10.0	D	7.27	18.00	1.44

\* Citric acid monohydrate

\*\* DMSO (instead of MeOH)

### Salt metathesis reactions

#### **Example 1: Nicotinamide-β-D-ribofuranoside L-ascorbate**

4.50 g (26 mmol) of L-ascorbic acid were suspended in 22.5 mL of methanol while stirring. The colorless suspension was cooled in an ice bath and 3.64 mL (26 mmol, 1 eq) of triethylamine were added. 27.5 mL of a 0.93 M solution of Et<sub>3</sub>N·L-ascorbate were prepared. 5.00 g (14.9 mmol, 1 eq) of nicotinamide-β-D-ribofuranoside bromide were dissolved with stirring in 3.0 mL of water at RT. 10 mL of methanol and 16 mL (14.9 mmol, 1 eq) of the above prepared solution of triethylammonium L-ascorbate were added. The yellow-orange solution was dropped slowly to 375 mL of ethanol, wherein a yellow flocculent suspension was produced. The suspension was stirred for a few h at RT.

The product was filtered, washed with ethanol, and dried under vacuum at 35 °C. Nicotinamide- $\beta$ -D-ribofuranoside L-ascorbate was isolated as a yellow powder (3.45 g, 54%).

3.11 g (7.22 mmol) of crude nicotinamide- $\beta$ -D-ribofuranoside L-ascorbate were dissolved in 1.9 mL of water. The orange clear solution was diluted with 16 mL of methanol. The solution was dropped slowly to 238 mL of ethanol, wherein an orange suspension was produced. Nicotinamide- $\beta$ -D-ribofuranoside L-ascorbate was isolated by filtration and dried at 35 °C. Nicotinamide- $\beta$ -D-ribofuranoside L-ascorbate was isolated as a yellowish powder (1.13 g, 36%). IC: Residual bromide 0.38%.

$^1\text{H}$ -NMR (400 MHz,  $\text{D}_2\text{O}$ ): 3.82 (br dd, 1H,  $J = 12.9$  Hz, 3.2 Hz,  $\text{H5}'\text{A}$ ), 3.97 (br d, 1H,  $\text{H5}'\text{B}$ ), 4.28 (t, 1H,  $J = 4.3$  Hz,  $\text{H3}'$ ), 4.34-4.47 (m, 2H,  $\text{H4}'$ ,  $\text{H2}'$ ), 6.17 (d, 1H,  $J = 4.2$  Hz,  $\text{H1}'$ ), 8.20 (t, 1H,  $J = 7.2$  Hz,  $\text{H5}$ ), 8.89 (br d, 1H,  $J = 7.8$  Hz,  $\text{H4}$ ), 9.19 (br d, 1H,  $J = 6.0$  Hz,  $\text{H6}$ ), 9.52 (s, 1H,  $\text{H2}$ ); Ascorbate: 3.58-3.70 (m, 2H), 3.92-3.97 (m, 1H), 4.40-4.46 (m, 1H). Impurities: 16 mol% nicotinamide: 7.49 (t, 1H), 8.14 (d,  $J = 8.2$  Hz, 1H), 8.60 (d, 1H), 8.82 (s, 1H); no  $\text{Et}_3\text{N}$  salt. Solvents: 1.3 mol% methanol: 3.26 (s, 3H); 46 mol% ethanol: 1.08 (t, 3H), 3.55 (q, 2H).

$^{13}\text{C}$ -NMR (100 MHz,  $\text{D}_2\text{O}$ ): 60.2 ( $\text{C5}'$ ), 69.8 ( $\text{C3}'$ ), 77.4 ( $\text{C2}'$ ), 87.7 ( $\text{C4}'$ ), 99.9 ( $\text{C1}'$ ), 128.4 ( $\text{C5}$ ), 133.9 ( $\text{C3}$ ), 140.4 ( $\text{C2}$ ), 142.6 ( $\text{C6}$ ), 145.6 ( $\text{C4}$ ), 165.7 ( $\text{CONH}_2$ ); Ascorbate: 62.5, 69.5, 78.2, 113.3, 174.6, 177.2. Impurities: nicotinamide: 124.2, 129.3, 136.5, 147.6, 151.7. Solvents: 16.8, 57.4 (ethanol).

#### Example 2: Nicotinamide- $\beta$ -D-ribofuranoside citrate

5.52 g (26.3 mmol) of citric acid monohydrate were dissolved in 55 mL of DMSO while stirring. The colorless solution was cooled in an ice bath and 12 mL (86 mmol, 3.27 eq) of triethylamine were added. 73 mL of a 0.36 molar solution of  $(\text{Et}_3\text{N})_3\cdot\text{citrate}$  were prepared. 9.00 g (26.8 mmol, 1.02 eq) of nicotinamide- $\beta$ -D-ribofuranoside bromide were suspended in 18 mL of DMSO. 73 mL (26.3 mmol, 1 eq) of the above produced solution were added and heated to 55 °C. The brownish solution was added to 1125 mL isopropanol, wherein a white suspension was produced. The solid was isolated by filtration and dried at 35 °C. Nicotinamide- $\beta$ -D-ribofuranoside citrate was isolated as a light-yellow powder (6.32 g, 75%).

3.22 g of crude nicotinamide- $\beta$ -D-ribofuranoside citrate were dissolved in a solution of 16 mL of methanol and 2 mL of water. The formed solution was dropped to 220 mL of isopropanol, wherein a white suspension was produced. The solid was isolated by filtration, washed with isopropanol and dried in vacuo at 35 °C. Nicotinamide- $\beta$ -D-ribofuranoside citrate was isolated as a white powder (2.67 g, 83%). IC: Residual bromide 0.19%.

$^1\text{H}$ -NMR (400 MHz,  $\text{D}_2\text{O}$ ): 2.54-2.68 (m, 4H,  $\text{CH}_2$ , citrate), 3.82 (dd, 3H,  $J = 13.0$ , 3.5 Hz,  $\text{H5}'\text{A}$ ), 3.97 (dd, 3H,  $J = 13.0$ , 2.9 Hz,  $\text{H5}'\text{B}$ ), 4.26-4.29 (m, 3H,  $\text{H3}'$ ), 4.40 (q, 3H,  $J = 3.3$  Hz,  $\text{H4}'$ ), 4.44 (t, 3H,  $J = 4.7$  Hz,  $\text{H2}'$ ), 6.17 (d, 3H,  $J = 4.4$  Hz,  $\text{H1}'$ ), 8.21 (dd, 3H,  $J = 8.2$ , 6.3 Hz,  $\text{H5}$ ), 8.90 (d, 3H,  $J = 8.2$  Hz,  $\text{H4}$ ), 9.20 (d, 3H,  $J = 6.3$  Hz,  $\text{H6}$ ), 9.52 (s, 3H,  $\text{H2}$ ). Impurities: 6 mol% nicotinamide: 7.50 (dd, 1H), 8.15 (m, 1H), 8.61 (d, 1H), 8.82 (s, 1H); 1.5 mol%  $\text{Et}_3\text{N}$  salt: 1.19 (t, 9H), 3.11 (q, 6H). Solvents: 31 mol% methanol: 3.26 (s, 3H); 18 mol% isopropanol: 1.07 (d, 6H), 3.92 (m, 1H).

$^{13}\text{C}$ -NMR (100 MHz,  $\text{D}_2\text{O}$ ): 44.6 ( $\text{CH}_2$ , citrate), 60.2 ( $\text{C5}'$ ), 69.7 ( $\text{C3}'$ ), 74.4 ( $\text{C3}$ , citrate), 77.4 ( $\text{C2}'$ ), 87.7 ( $\text{C4}'$ ), 99.9 ( $\text{C1}'$ ), 128.4 ( $\text{C5}$ ), 133.9 ( $\text{C3}$ ), 140.4 ( $\text{C2}$ ), 142.6 ( $\text{C6}$ ), 145.6 ( $\text{C4}$ ), 165.7 ( $\text{CONH}_2$ ), 176.9 (2x  $\text{COO}$ , citrate), 180.0 ( $\text{COO}$ , citrate). Impurities: Nicotinamide: 124.3, 136.7, 147.5, 151.6;  $\text{Et}_3\text{N}$  salt: 8.2, 46.6. Solvents: 48.9 (methanol); 23.7, 64.2 (isopropanol).

#### Example 3: Salt metathesis experiments where spontaneous crystallization of nicotinamide- $\beta$ -D-ribofuranoside bromide occurred

### Nicotinamide- $\beta$ -D-ribofuranoside formiate

1.40 mL (36 mmol, 1 eq) of formic acid were dissolved in 10 mL of methanol while stirring. The colorless solution was cooled in an ice bath and 5.0 mL (36 mmol, 1 eq) of triethylamine were added. 15 mL of a 2.40 M solution of Et<sub>3</sub>N-formiate were prepared. 10.0 g of nicotinamide- $\beta$ -D-ribofuranoside bromide (29.8 mmol) were suspended in 25 mL of methanol. 12.5 mL (30 mmol, 1 eq) of the triethylammonium formiate solution prepared according to the above procedure were added and the suspension heated to 50 °C until all solid dissolved, generating a slightly yellow solution. By storing this at 4 °C for 16 h, crystallization occurred. The formed solid was filtered and washed with ethanol. In the mother liquor additional crystals appeared and were filtered likewise. The combined solids were dried in vacuum at 35 °C, obtaining 6.21 g (62%) of white crystalline nicotinamide- $\beta$ -D-ribofuranoside bromide.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): 3.88 (dd, 1H, *J* = 12.9, 3.6 Hz, H5'A), 4.02 (dd, 1H, *J* = 12.9, 2.9 Hz, H5'B), 4.33-4.36 (m, 1H, H3'), 4.45 (q, 1H, *J* = 3.6 Hz, H4'), 4.52 (t, 1H, *J* = 4.7 Hz, H2'), 6.24 (d, 1H, *J* = 4.4 Hz, H1'), 8.28 (dd, 1H, *J* = 8.0, 6.3 Hz, H5), 8.96 (d, 1H, *J* = 7.7 Hz, H4), 9.26 (d, 1H, *J* = 6.2 Hz, H6), 9.57 (s, 1H, H2). Impurities: 1 mol% nicotinamide; 0.3 mol% Et<sub>3</sub>N salt: 1.26 (t, 9H), 3.18 (q, 6H). Solvents: 2.4 mol% methanol: 3.31 (s, 3H).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): 60.3 (C5'), 69.8 (C3'), 77.4 (C2'), 87.7 (C4'), 100.0 (C1'), 128.6 (C5), 134.0 (C3), 140.4 (C2), 142.7 (C6), 145.7 (C4), 165.8 (CONH<sub>2</sub>). Solvents: 49.0 (methanol).

Experiments with maleic acid and salicylic acid behaved similarly.

### Example 4: Nicotinamide- $\beta$ -D-ribofuranoside D-glucuronate

5.10 g (26 mmol, 1 eq) of D-glucuronic acid were suspended in 15 mL of methanol while stirring. The colorless suspension was cooled in an ice bath and 3.60 mL (25.8 mmol, 0.99 eq) of triethylamine were added. 19.5 mL of a 1.32 molar solution of Et<sub>3</sub>N·D-glucuronate were prepared. 5.00 g (14.9 mmol) of nicotinamide- $\beta$ -D-ribofuranoside bromide were dissolved while stirring in 3.0 mL of water at RT, and 10 mL of methanol were added. 11.3 mL (14.9 mmol, 1 eq) of the above prepared solution of triethylammonium D-glucuronate were added. The clear yellowish solution was dropped slowly to 455 mL of *n*-butanol, wherein a white suspension was produced. The suspension was stirred for further five h at RT. The product was filtered, washed with isopropanol, and dried in vacuo at 35 °C. Nicotinamide- $\beta$ -D-ribofuranoside D-glucuronate (6.64 g, 99 %) was dissolved in 6.6 mL of water and diluted with 33 mL of methanol. The yellowish solution was dropped to 550 mL of *n*-butanol, wherein a white suspension was produced. The suspension was filtered, the residue was washed with isopropanol and dried at 35 °C. Nicotinamide- $\beta$ -D-ribofuranoside D-glucuronate was isolated as a white powder (5.19 g, 78%). Mp. 66–76 °C; residual bromide 1.43% (IC).

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): NR: 3.88 (dd, 1H, *J* = 13.0, 3.5 Hz, H5'A), 4.03 (dd, 1H, *J* = 13.0, 2.9 Hz, H5'B), 4.32-4.35 (m, 1H, H3'), 4.46 (q, 1H, *J* = 3.4 Hz, H4'), 4.49 (t, 1H, *J* = 4.8 Hz, H2'), 6.23 (d, 1H, *J* = 4.4 Hz, H1'), 8.26 (dd, 1H, *J* = 8.1, 6.3 Hz, H5), 8.96 (dt, 1H, *J* = 8.1, 1.4 Hz, H4), 9.25 (d, 1H, *J* = 6.3 Hz, H6), 9.58 (s, 1H, H2); GlcUA (anomeric mixture): 3.21-3.27 (m), 3.44-3.49 (m), 3.50-3.57 (m), 3.65-3.71 (m), 4.00 (t), 4.60 (d, *J* = 7.9 Hz,  $\beta$ -anomer), 5.20 (d, *J* = 3.8 Hz,  $\alpha$ -anomer). Impurities: 2 mol% nicotinamide: 7.61 (dd, 1H), 8.69 (d, 1H); 0.9 mol% Et<sub>3</sub>N salt: 1.25 (t, 9H), 3.17 (q, 6H). Solvents: 23 mol% methanol: 3.31 (s, 3H); 5.7 mol% butanol: 0.86 (t, 3H, H4), 1.30 (m, 2H, H3), 1.48 (m, 2H, H2).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): NR: 60.2 (C5'), 69.8 (C3'), 77.4 (C2'), 87.7 (C4'), 99.9 (C1'), 128.4 (C5), 133.9 (C3), 140.4 (C2), 142.6 (C6), 145.6 (C4), 165.8 (CONH<sub>2</sub>); GlcUA: 71.3, 71.7, 71.8, 72.0, 72.5, 74.0, 75.5, 76.1, 92.1, 95.9, 175.7, 176.7. Solvents: 48.9 (methanol); 13.1, 18.4, 33.4, 61.5 (*n*-butanol).

**Example 5: Salt metathesis experiments where nicotinamide- $\beta$ -D-ribofuranoside bromide crystallized during precipitation in alcohol or during addition to longer chain alcohols**

**Nicotinamide- $\beta$ -D-ribofuranoside L-lactate**

2.34 g (26 mmol) of L-lactic acid were dissolved in 10 mL of methanol while stirring. The almost colorless solution was cooled in an ice bath and 3.64 mL (26 mmol, 1 eq) of triethylamine added. 15 mL of a 1.73 molar solution of Et<sub>3</sub>N·L-lactate were prepared. 5.80 g (17.3 mmol) nicotinamide- $\beta$ -D-ribofuranoside bromide were suspended in 20 mL methanol. 10 mL (17.3 mmol, 1 eq) of the triethylammonium L-lactate solution prepared according to the above instructions were added and the suspension heated to 50 °C until all solid dissolved. The slightly yellowish, viscous solution was slowly dropped to 400 mL of isopropanol, producing a white, crystalline suspension. The solid was filtered after a few h of stirring, washed with isopropanol and dried in vacuo at 35 °C. A white crystalline powder was obtained (4.27 g, 73 %). NMR showed that nicotinamide- $\beta$ -D-ribofuranoside bromide had crystallized. IC: 24.4 % bromide.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): 3.87 (dd, 1H, *J* = 12.9, 3.6 Hz, H5'A), 4.01 (dd, 1H, *J* = 12.9, 2.9 Hz, H5'B), 4.33-4.36 (m, 1H, H3'), 4.44 (q, 1H, *J* = 3.4 Hz, H4'), 4.50 (t, 1H, *J* = 4.7 Hz, H2'), 6.22 (d, 1H, *J* = 4.4 Hz, H1'), 8.25 (dd, 1H, *J* = 8.1, 6.3 Hz, H5), 8.95 (dt, 1H, *J* = 8.1, 1.5 Hz, H4), 9.24 (d, 1H, *J* = 6.3 Hz, H6), 9.56 (s, 1H, H2). Impurities: < 1 mol% nicotinamide; 0.3 mol% Et<sub>3</sub>N salt: 1.26 (t, 9H), 3.17 (q, 6H). Solvents: 1.5 mol% isopropanol: 1.11 (d, 6H).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): 60.2 (C5'), 69.8 (C3'), 77.4 (C2'), 87.7 (C4'), 100.0 (C1'), 128.5 (C5), 134.0 (C3), 140.4 (C2), 142.7 (C6), 145.7 (C4), 165.8 (CONH<sub>2</sub>). Solvents: 23.8 (iso-propanol).

Experiments with malonic acid, methanesulfonic acid and sorbic acid behaved similarly.

**Example 6: Nicotinamide- $\beta$ -D-ribofuranoside L-malate**

3.50 g (26 mmol) of L-malic acid were dissolved in 10 mL of methanol while stirring. The almost colorless solution was cooled in an ice bath and 7.30 mL (52 mmol, 2 eq) of triethylamine were added. 18 mL of a 1.45 molar solution of (Et<sub>3</sub>N)<sub>2</sub>·L-malate were prepared. 5.00 g (14.9 mmol) of nicotinamide- $\beta$ -D-ribofuranoside bromide were suspended in 15 mL of methanol. 10.3 mL (14.9 mmol, 1 eq) of the triethylammonium L-malate solution prepared according to the above instructions were added and the suspension heated to 50 °C until all solid dissolved. The slightly yellowish, viscous solution (28 mL) was slowly dropped to 280 mL of isopropanol, producing a white, flaky suspension. The solid was filtered after a few hours of stirring, washed with isopropanol and dried in vacuum at 35 °C. Nicotinamide- $\beta$ -D-ribofuranoside L-malate was isolated as a white powder (4.51 g, quantitative yield). 1.80 g of crude nicotinamide- $\beta$ -D-ribofuranoside L-malate were dissolved in 1.1 mL of water and diluted with 9 mL of methanol. The solution was slowly dropped to 125 mL of isopropanol, wherein a white flocculent suspension was produced. After a few hours, the solid was isolated by filtration, washed with isopropanol and dried in vacuo at 35 °C. Nicotinamide- $\beta$ -D-ribofuranoside L-malate was isolated as a white powder (1.46 g, 81%). Mp: 63–68 °C. IC: Residual bromide 2.18%.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): 2.35 (dd, 1H, *J* = 15.6, 9.5 Hz, CH<sub>2</sub>, malate), 2.63 (dd, 1H, *J* = 15.6, 3.4 Hz, CH<sub>2</sub>, malate), 3.83 (dd, 2H, *J* = 12.9, 3.5 Hz, H5'A), 3.98 (dd, 2H, *J* = 12.9, 2.9 Hz, H5'B), 4.22 (dd, 1H, *J* = 9.5, 3.4 Hz, CHOH, malate), 4.27-4.30 (m, 2H, H3'), 4.41 (q, *J* = 3.3 Hz, 2H, H4'), 4.44 (t, 2H, *J* = 4.8 Hz, H2'), 6.18 (d, 2H, *J* = 4.4 Hz, H1'), 8.21 (dd, 2H, 8.1, 6.1 Hz, H5), 8.91 (dt, 2H, *J* = 8.1, 1.5 Hz, H4), 9.20 (d, 2H, *J* = 6.1 Hz, H6), 9.53 (s, 2H, H2). Impurities: 22 mol% nicotinamide: 7.49 (dd, 1H), 8.14 (m, 1H), 8.60 (d, 1H), 8.81 (s, 1H); 0.45 mol% Et<sub>3</sub>N salt: 1.19 (t, 9H), 3.11 (q, 6H). Solvents: 16 mol% methanol: 3.26 (s, 3H); 17.3 mol% iso-propanol: 1.08 (d, 6H), 3.92 (m, 1H).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): 41.8 (CH<sub>2</sub>, malate), 60.2 (C5'), 69.8 (CHOH, malate), 69.8 (C3'), 77.4 (C2'), 87.7 (C4'), 99.9 (C1'), 128.4 (C5), 133.9 (C3), 140.4 (C2), 142.6 (C6), 145.6 (C4), 165.7 (CONH<sub>2</sub>), 178.6



(COO, malate), 180.4 (COO, malate). Impurity nicotinamide: 124.3, 136.6, 147.5, 151.6. Solvents: 48.9 (methanol); 23.7, 64.2 (iso-propanol).

#### Example 7: Nicotinamide- $\beta$ -D-ribofuranoside L-tartrate

3.90 g (26.1 mmol) of L-tartaric acid were dissolved in 10 mL of methanol while stirring. The almost colorless solution was cooled in an ice bath and 7.30 mL (52.2 mmol, 2 eq) of triethylamine were added. 18 mL of a 1.44 molar solution of  $(\text{Et}_3\text{N})_2\cdot\text{L-tartrate}$  were prepared. 9.65 g (28.8 mmol, 2 eq) of nicotinamide- $\beta$ -D-ribofuranoside bromide were dissolved in 5.8 mL of water and the solution was diluted with 20 mL of methanol. 10 mL (14.4 mmol) of the triethylammonium L-tartrate solution prepared according to the above instructions were added. The slightly yellowish, viscous solution (40 mL) was slowly dropped to 500 mL of ethanol, producing a white, fine suspension. The solid was filtered after an hour of stirring, washed with ethanol, and dried in vacuum at 35 °C. Nicotinamide- $\beta$ -D-ribofuranoside L-tartrate was isolated as a white powder (8.06 g, 85%). 7.72 g of crude nicotinamide- $\beta$ -D-ribofuranoside L-tartrate were dissolved in 7.7 mL of water and diluted with 38 mL of methanol. The colorless solution was slowly dropped to 600 mL of ethanol, wherein a white flocculent suspension was produced. After an h the solid was isolated by filtration, washed with ethanol and dried in vacuo at 35 °C. Nicotinamide- $\beta$ -D-ribofuranoside L-tartrate was isolated as a white powder (5.16 g, 67%). IC: Residual bromide 0.55 %.

$^1\text{H-NMR}$  (400 MHz,  $\text{D}_2\text{O}$ ): 3.83 (dd, 2H,  $J = 12.9, 3.5$  Hz,  $\text{H5}'\text{A}$ ), 3.98 (dd, 2H,  $J = 12.9, 2.8$  Hz,  $\text{H5}'\text{B}$ ), 4.25 (s, 2H, 2 x CHOH, tartrate), 4.29 (t, 2H,  $J = 4.7$  Hz,  $\text{H3}'$ ), 4.39-4.42 (m, 2H,  $\text{H4}'$ ), 4.45 (t, 2H,  $J = 4.7$  Hz,  $\text{H2}'$ ), 6.18 (d, 2H,  $J = 4.4$  Hz,  $\text{H1}'$ ), 8.21 (dd, 2H,  $J = 8.1, 6.3$  Hz,  $\text{H5}$ ), 8.91 (dt, 2H,  $J = 8.1, 1.5$  Hz,  $\text{H4}$ ), 9.21 (d, 2H,  $J = 6.3$  Hz,  $\text{H6}$ ), 9.53 (s, 2H,  $\text{H2}$ ). Impurities: 10 mol% nicotinamide: 7.51 (dd, 1H), 8.16 (m, 1H), 8.61 (d, 1H), 8.82 (s, 1H); 0.1 mol%  $\text{Et}_3\text{N}$  salt: 1.20 (t, 9H), 3.12 (q, 6H). Solvents: 3 mol% methanol: 3.27 (s, 3H); 33 mol% ethanol: 1.09 (t, 3H), 3.56 (q, 2H).

$^{13}\text{C-NMR}$  (100 MHz,  $\text{D}_2\text{O}$ ): 60.2 ( $\text{C5}'$ ), 69.7 ( $\text{C3}'$ ), 73.7 (2x CHOH, tartrate), 77.4 ( $\text{C2}'$ ), 87.7 ( $\text{C4}'$ ), 99.9 ( $\text{C1}'$ ), 128.4 ( $\text{C5}$ ), 133.9 ( $\text{C3}$ ), 140.4 ( $\text{C2}$ ), 142.6 ( $\text{C6}$ ), 145.6 ( $\text{C4}$ ), 165.8 ( $\text{CONH}_2$ ), 178.0 (2 x COO, tartrate). Impurities: Nicotinamide: 124.4, 129.4, 136.9, 147.3, 151.4;  $\text{Et}_3\text{N}$  salt: 8.2, 46.6. Solvent ethanol: 16.8, 57.4.

## Section S2: Preparation of acidic salts

### Preparation of a solution of $\text{Et}_3\text{N}\cdot\text{hydrogen dicarboxylate}$ ( $\text{Et}_3\text{N}\cdot\text{HA}$ ):

The amount of dicarboxylic acid  $\text{H}_2\text{A}$  (or citric acid) (26.0 mmol) shown in the table was suspended (S) or dissolved (D) in methanol (MeOH) while stirring at RT. The yellowish suspension or solution was cooled at 0 °C and triethylamine ( $\text{Et}_3\text{N}$ ) was added, which caused a slight temperature increase. In some cases, presence of solid was observed due to poor solubilization or crystallization of the  $\text{Et}_3\text{N}$  salt. In these cases, the indicated amount of water ( $\text{H}_2\text{O}$ ) was added to the suspension. The pH of the still slightly yellowish solutions was 4–4.5, with the exception of the hydrogen citrate solution, where the pH was about 6. Thus, approximately x mL of y molar  $\text{Et}_3\text{N}\cdot\text{hydrogen dicarboxylate}$  solution ( $\text{Et}_3\text{N}\cdot\text{HA}$ ) were obtained (Table S2).

Table S2: Dicarboxylates used to prepare the  $\text{Et}_3\text{N}\cdot\text{HA}$  solutions.

Dicarboxylate	Amount Acid (g)	MeOH (mL)	S / D	$\text{Et}_3\text{N}$ (mL)	$\text{H}_2\text{O}$ (mL)	x (mL)	y (M)
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Hydrogen citrate	5.50*	10	D	7.30	-	~19	1.38
Dihydrogen citrate	5.50*	10	D	3.65	5.5	~21.5	1.22
Hydrogen fumarate	3.02	10	S	3.64	-	~15	1.73
Hydrogen maleate	3.02	10	D	3.64	-	~15	1.73
D-Hydrogen malate	3.50	10	D	3.64	-	~15	1.73
L-Hydrogen malate	3.50	10	D	3.64	-	~15	1.73
DL-Hydrogen malate	3.50	10	D	3.64	-	~15	1.73
Hydrogen malonate	2.70	10	D	3.64	-	~14.5	1.80
H-mercaptosuccinate	3.90	10	D	3.64	-	~15	1.73
Hydrogen ketoglutarate	3.80	10	D	3.74	-	~15	1.73
Hydrogen oxalacetate	3.43	10	D	3.64	-	~14.5	1.79
Hydrogen oxalate	2.34	10	D	3.64	0.5	~14	1.85
Hydrogen succinate	3.07	10	S	3.64	-	~15	1.73
D-Hydrogen tartrate	3.92	10	D	3.64	-	~15	1.73
L-Hydrogen tartrate	3.92	10	D	3.64	-	~15	1.73
DL-Hydrogen tartrate	3.92	10	D	3.64	-	~15	1.73
meso-Hydrogen tartrate	2.25**	5	D	1.82	-	~ 7.7	1.69
Hydrogen tartronate	3.12	10	D	3.64	-	~14.5	1.79

\* Citric acid monohydrate

\*\* meso-Tartaric acid monohydrate

### Non-crystalline Salts

#### **Example 8: Preparation of nicotinamide- $\beta$ -D-ribofuranoside dihydrogen citrate**

5.50 g (26.2 mmol) of citric acid monohydrate were dissolved in 10 mL of methanol and 5.5 mL of water while stirring. The colorless solution was cooled in an ice bath and 3.65 mL (26.2 mmol, 1 eq) of triethylamine added. 21.5 mL of a 1.22 molar solution of Et<sub>3</sub>N-dihydrogen citrate were prepared. 0.41 g (1.22 mmol) of nicotinamide- $\beta$ -D-ribofuranoside bromide were suspended in 1 mL of methanol upon stirring. 1 mL (1.22 mmol, 1 eq) of the 1.22 M solution of triethylammonium dihydrogen citrate was added. The suspension was heated at reflux and was then cooled down. The colorless and clear solution was dropped into 38 mL of isopropanol. The formed suspension was filtered, and the residue was dried at room temperature in vacuo. 0.23 g (42 %) of a white hygroscopic powder were obtained, which melted during drying and was therefore not further investigated.

#### **Example 9: Preparation of nicotinamide- $\beta$ -D-ribofuranoside meso-hydrogen tartrate**

2.25 g (13.0 mmol) of meso-tartaric acid monohydrate 97% were dissolved in 5 mL of methanol with stirring. The colorless solution was cooled in an ice bath and 1.82 mL (13.0 mmol, 1 eq) of triethylamine added. 7.7 mL of a 1.69 M solution of Et<sub>3</sub>N-meso-hydrogen tartrate were prepared. 0.57 g (1.70 mmol) of nicotinamide- $\beta$ -D-ribofuranoside bromide were suspended in 1 mL of methanol upon stirring. 1 mL (1.69 mmol, 1 eq) of the 1.69 molar solution of triethylammonium meso-hydrogen tartrate was added. The suspension was heated to the boiling point and was then cooled down. The formed emulsion was slightly warmed up, and the clear solution dropped into 20

mL of ethanol. The formed suspension was filtered, and the residue was dried at room temperature in vacuo. Nicotinamide- $\beta$ -D-ribofuranoside meso-hydrogen tartrate was isolated as a flaky, hygroscopic powder (0.44 g, 62%).

$^1\text{H-NMR}$  (400 MHz,  $\text{D}_2\text{O}$ ): 3.82 (dd, 1H,  $J = 12.9, 3.5$  Hz,  $\text{H5}'\text{A}$ ), 3.97 (dd, 1H,  $J = 12.9, 2.8$  Hz,  $\text{H5}'\text{B}$ ), 4.28 (m, 1H,  $\text{H3}'$ ), 4.35 (s, 2H, 2  $\times$  CHOH, meso-H-tartrate), 4.40 (m, 1H,  $\text{H4}'$ ), 4.44 (t, 1H,  $J = 4.7$  Hz,  $\text{H2}'$ ), 6.18 (d, 1H,  $J = 4.5$  Hz,  $\text{H1}'$ ), 8.21 (t, 1H,  $J = 7.0$  Hz,  $\text{H5}$ ), 8.91 (d, 1H,  $J = 8.2$  Hz,  $\text{H4}$ ), 9.20 (d, 1H,  $J = 6.2$  Hz,  $\text{H6}$ ), 9.53 (s, 1H,  $\text{H2}$ ). Impurities: 5 mol% nicotinamide: 7.65 (dd, 1H), 8.33 (d, 1H), 8.67 (d, 1H); 10 mol%  $\text{Et}_3\text{N}$  salt: 1.20 (t, 9H), 3.12 (q, 6H). Solvents: 16 mol% methanol: 3.26 (s, 3H); 40 mol% ethanol: 1.09 (t, 3H), 3.56 (q, 2H).

$^{13}\text{C-NMR}$  (100 MHz,  $\text{D}_2\text{O}$ ): 60.2 ( $\text{C5}'$ ), 69.7 ( $\text{C3}'$ ), 73.7 (2  $\times$  CHOH, meso-H-tartrate), 77.4 ( $\text{C2}'$ ), 87.7 ( $\text{C4}'$ ), 99.9 ( $\text{C1}'$ ), 128.4 ( $\text{C5}$ ), 133.9 ( $\text{C3}$ ), 140.4 ( $\text{C2}$ ), 142.6 ( $\text{C6}$ ), 145.6 ( $\text{C4}$ ), 165.8 ( $\text{CONH}_2$ ), 175.7 (2  $\times$  COO, meso-H-tartrate). Impurities: Nicotinamide: 125.0, 138.6, 146.0, 149.8;  $\text{Et}_3\text{N}$  salt: 8.2, 46.6. Solvents: 48.9 (methanol); 16.8, 57.4 (ethanol).

### Crystalline Salts from Nicotinamide- $\beta$ -D-ribofuranoside bromide

#### **Example 10: Preparation of nicotinamide- $\beta$ -D-ribofuranoside L-hydrogen tartrate from nicotinamide- $\beta$ -D-ribofuranoside bromide using various ammonium L-hydrogen tartrate salts for salt metathesis**

##### **Example 10a: Use of triethylammonium-L-hydrogen tartrate**

3.92 g (26.1 mmol) of L-tartaric acid were dissolved in 10 mL of methanol while stirring. The colorless solution was cooled in an ice bath, and 3.64 mL triethylamine (26.1 mmol, 1 eq) were added. The pH of the slightly yellowish solution was around 4–4.5. 15 mL of a 1.73 M solution of  $\text{Et}_3\text{N}$ -L-hydrogen tartrate were prepared. 5.80 g (17.3 mmol) of nicotinamide- $\beta$ -D-ribofuranoside bromide were dissolved while stirring in 3.5 mL water at room temperature, and 10 mL of methanol were added. 10 mL (17.3 mmol, 1 eq) of the above prepared solution of triethylammonium L-hydrogen tartrate were added to the clear colorless solution. The formed white suspension was stirred for a further hour at room temperature. The product was filtered, washed with methanol and dried in vacuo at 35 °C. Nicotinamide-beta-D-ribofuranoside-L-hydrogen tartrate was isolated as a white, crystalline powder (6.62 g, 95%). Mp: 129–130°C; IC: Residual bromide 0.20 %.

$^1\text{H-NMR}$  (400 MHz,  $\text{D}_2\text{O}$ ): 3.82 (dd, 1H,  $J = 12.9, 3.5$  Hz,  $\text{H5}'\text{A}$ ), 3.96 (dd, 1H,  $J = 12.9, 2.9$  Hz,  $\text{H5}'\text{B}$ ), 4.28 (t, 1H,  $J = 4.6$  Hz,  $\text{H3}'$ ), 4.38 – 4.46 (m, 2H,  $\text{H2}'$ ,  $\text{H4}'$ ), 4.41 (s, 2H, 2  $\times$  CHOH, H-tartrate), 6.17 (d, 1H,  $J = 4.4$  Hz,  $\text{H1}'$ ), 8.20 (dd, 1H,  $J = 8.1, 6.3$  Hz,  $\text{H5}$ ), 8.90 (dt, 1H,  $J = 8.1, 1.5$  Hz,  $\text{H4}$ ), 9.19 (d, 1H,  $J = 6.2$  Hz,  $\text{H6}$ ), 9.52 (s, 1H,  $\text{H2}$ ). Impurities: < 1 mol% nicotinamide; 1.2 mol%  $\text{Et}_3\text{N}$  salt: 1.19 (t, 9H), 3.11 (q, 6H). Solvents: 7.3 mol% methanol: 3.25 (s, 3H).

$^{13}\text{C-NMR}$  (100 MHz,  $\text{D}_2\text{O}$ ): 60.2 ( $\text{C5}'$ ), 69.7 ( $\text{C3}'$ ), 72.8 (2 $\times$  CHOH, H-tartrate), 77.4 ( $\text{C2}'$ ), 87.6 ( $\text{C4}'$ ), 99.9 ( $\text{C1}'$ ), 128.4 ( $\text{C5}$ ), 133.9 ( $\text{C3}$ ), 140.4 ( $\text{C2}$ ), 142.6 ( $\text{C6}$ ), 145.6 ( $\text{C4}$ ), 165.8 ( $\text{CONH}_2$ ), 176.3 (2  $\times$  COO, H-tartrate). Impurity: 8.2, 46.6 ( $\text{Et}_3\text{N}$ ). Solvents: 48.9 (methanol).

##### **Example 10b: Use of tributylammonium-L-hydrogen tartrate**

3.92 g (26.1 mmol) of L-tartaric acid were dissolved in 10 mL of methanol with stirring. The colorless solution was cooled in an ice bath and 6.3 mL tributylamine (26.0 mmol, 1 eq) added. The pH of the slightly yellowish solution was around 4. In this manner 17.5 mL of a 1.49 molar solution of tributylammonium L-hydrogen tartrate was prepared. 5.80 g (17.3 mmol) of nicotinamide- $\beta$ -D-ribofuranoside bromide were dissolved while stirring in 3.5 mL water at room temperature, and

10 mL of methanol were added. 11.6 mL (17.3 mmol, 1 eq) of the above prepared solution of tributylammonium L-hydrogen tartrate were added to the clear colorless solution. White product immediately starts crystallizing, and the suspension was stirred for a further hour at room temperature. The product was filtered, washed with methanol and dried in vacuum at 35 °C. Nicotinamide-beta-D-ribofuranoside-L-hydrogen tartrate was isolated as a white, crystalline powder (6.37 g, 91%). Mp. 128 °C; IC: Residual bromide 0.62%.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): Analogous to Example 10a. Impurities: < 1 mol% nicotinamide, 2.7 mol% Bu<sub>3</sub>N salt: 0.84 (t, 9H), 1.28 (m, 6H), 1.58 (m, 6H), 3.04 (q, 6H); solvents: 3.7 mol% methanol: 3.25 (s, 3H).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): Analogous to Example 10a.

#### **Example 10c: Use of tetrabutylammonium-L-hydrogen tartrate**

3.92 g (26.1 mmol) of L-tartaric acid were dissolved in 10 mL methanol while stirring. The colorless solution was cooled in an ice bath and 17.1 mL (26.1 mmol, 1 eq) of a 40% solution of tetrabutylammonium hydroxide in water were added. The pH of the slightly yellowish solution was around 4. 29 mL of a 0.9 M solution of tetrabutylammonium L-hydrogen tartrate were prepared. 5.80 g (17.3 mmol) of nicotinamide-β-D-ribofuranoside bromide were dissolved while stirring in 3.5 mL of water at room temperature, and 10 mL of methanol were added. 19.3 mL (17.3 mmol, 1 eq) of the above prepared solution of tetrabutylammonium L-hydrogen tartrate were added to the clear colorless solution. The formed white suspension was stirred for a further hour at room temperature. The product was filtered, washed with methanol and dried in vacuum at 35 °C. Nicotinamide-beta-D-ribofuranoside-L-hydrogen tartrate was isolated as a white, crystalline powder (5.60 g, 80%). Mp. 129–130°C; IC: Residual bromide 0.13%.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): Analogous to Example 10a. Impurities: < 1 mol% nicotinamide; 0.35 mol% Bu<sub>4</sub>N salt: 0.36 (t, 9H), 1.27 (m, 6H), 1.56 (m, 6H), 3.11 (q, 6H); solvents: 2.4 mol% methanol: 3.26 (s, 3H).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): Analogous to Example 10a.

#### **Example 11: Preparation of nicotinamide-β-D-ribofuranoside DL-hydrogen tartrate from nicotinamide-β-D-ribofuranoside bromide**

NR<sup>+</sup> DL-hydrogen tartrate was prepared analogously to Example 10a and isolated as a white, crystalline powder (6.30 g, 90%). Mp: 112–114°C; IC: Residual bromide 0.1%.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): 3.82 (dd, 1H, *J* = 12.9, 3.6 Hz, H5'A), 3.97 (dd, 1H, *J* = 12.9, 2.8 Hz, H5'B), 4.28 (t, 1H, *J* = 4.6 Hz, H3'), 4.38–4.46 (m, 2H, H2', H4'), 4.42 (s, 2H, 2 × CHOH, H-tartrate), 6.17 (d, 1H, *J* = 4.5 Hz, H1'), 8.20 (dd, 1H, *J* = 8.1, 6.2 Hz, H5), 8.90 (dt, 1H, *J* = 8.1, 1.4 Hz, H4), 9.19 (d, 1H, *J* = 6.3 Hz, H6), 9.52 (s, 1H, H2). Impurities: < 1 mol% nicotinamide; 0.7 mol% Et<sub>3</sub>N salt: 1.19 (t, 9H), 3.11 (q, 6H). Solvents: 3.3 mol% methanol: 3.25 (s, 3H).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): 60.2 (C5'), 69.7 (C3'), 72.8 (2 × CHOH, H-tartrate), 77.4 (C2'), 87.7 (C4'), 99.9 (C1'), 128.4 (C5), 133.9 (C3), 140.4 (C2), 142.6 (C6), 145.6 (C4), 165.8 (CONH2), 176.3 (2 × COO, H-tartrate). Impurity: 8.2 (Et<sub>3</sub>N). Solvents: 48.9 (methanol).

#### **Example 12: Preparation of nicotinamide-β-D-ribofuranoside L-hydrogen malate from nicotinamide-β-D-ribofuranoside bromide using various ammonium L-hydrogen malate salts for salt metathesis**

**Example 12a: Use of triethylammonium-L-hydrogen malate**

3.50 g (26.1 mmol) of L-malic acid were dissolved in 10 mL methanol with stirring. The solution was cooled in an ice bath and 3.64 mL of triethylamine (26.1 mmol, 1 eq) added. The pH of the slightly yellowish solution was around 4.5. 15 mL of a 1.73 molar solution of Et<sub>3</sub>N-L-hydrogen malate were prepared. 5.80 g (17.3 mmol) of nicotinamide-β-D-ribofuranoside bromide were suspended in 10 mL of methanol upon stirring. 10 mL (17.3 mmol, 1 eq) of the 1.73 molar solution of triethylammonium L-hydrogen malate were added. The suspension was heated until the solids dissolved completely. After cooling, a white solid precipitated. The suspension was stirred for 30 min and then filtered. The residue was washed with methanol and dried in vacuo at 35 °C. Nicotinamide-beta-D-ribofuranoside-L-hydrogen malate was isolated as a white crystalline powder (4.15 g, 62%). Mp: 116.5–117 °C. IC: Residual bromide 0.10%.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): 2.53 (dd, 1H, *J* = 16.0, 8.1 Hz, CH<sub>2</sub>, H-malate), 2.72 (dd, 1H, *J* = 16.0, 4.3 Hz, CH<sub>2</sub>, H-malate), 3.81 (dd, 1H, *J* = 12.9, 3.5 Hz, H5'A), 3.96 (dd, 1H, *J* = 12.9, 2.8 Hz, H5'B), 4.27 (m, 1H, H3'), 4.28 (m, 1H, CHOH, H-malate), 4.39 (q, *J* = 3.3 Hz, 1H, H4'), 4.43 (t, 1H, *J* = 4.7 Hz, H2'), 6.17 (d, 1H, *J* = 4.5 Hz, H1'), 8.20 (t, 1H, *J* = 6.9 Hz, H5), 8.90 (dt, 1H, *J* = 8.1, 1.4 Hz, H4), 9.19 (d, 1H, *J* = 6.3 Hz, H6), 9.52 (s, 1H, H2). Impurities: < 1 mol% nicotinamide; 0.7 mol% Et<sub>3</sub>N salt: 1.19 (t, 9H), 3.11 (q, 6H). Solvents: 6.3 mol% methanol: 3.25 (s, 3H).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): 40.0 (CH<sub>2</sub>, H-malate), 60.2 (C5'), 68.5 (CHOH, H-malate), 69.7 (C3'), 77.4 (C2'), 87.7 (C4'), 99.9 (C1'), 128.4 (C5), 133.9 (C3), 140.4 (C2), 142.6 (C6), 145.6 (C4), 165.7 (CONH<sub>2</sub>), 176.3 (COO, H-malate), 179.0 (COO, H-malate). Impurity Et<sub>3</sub>N salt: 8.2. Solvent: 48.9 (methanol).

**Example 12b: Use of tetrabutylammonium-L-hydrogen malate**

3.50 g (26.1 mmol) of L-malic acid were dissolved in 10 mL of methanol while stirring. The colorless solution was cooled in an ice bath and 6.23 mL of tributylamine (26.1 mmol, 1 eq) were added. The pH of the slightly yellowish solution was around 5. 17.5 mL of a 1.49 M solution of tributylammonium L-hydrogen malate were prepared. 5.80 g (17.3 mmol) of nicotinamide-β-D-ribofuranoside bromide were suspended in 17.5 mL of methanol upon stirring. 11.6 mL (17.3 mmol, 1 eq) of the above prepared solution of tributylammonium L-hydrogen malate were added. The suspension was heated until the solids dissolved completely. A white solid crystallized upon cooling. The suspension was stirred for 3 h and then filtered. The residue was washed with methanol and dried in vacuo at 35 °C. Nicotinamide-beta-D-ribofuranoside-L-hydrogen malate was isolated as a white crystalline powder (4.89 g, 73%). Mp. 115.5 °C; IC: Residual bromide 0.64%.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): Analogous to Example 12a. Impurities: < 1 mol% nicotinamide; 0.2 mol% Bu<sub>3</sub>N salt; 2 mol% methanol.

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): Analogous to Example 12a.

**Example 13: The following crystalline nicotinamide-β-D-ribofuranoside salts were prepared analogously to Example 12a**

**NR<sup>+</sup> D-hydrogen malate:** 4.01 g (60%) of a white, crystalline powder were obtained; Mp. 117.0-117.5 °C; IC: Residual bromide 0.90%.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): 2.54 (dd, 1H, *J* = 16.0, 8.1 Hz, CH<sub>2</sub>, H-malate), 2.72 (dd, 1H, *J* = 16.0, 4.3 Hz, CH<sub>2</sub>, H-malate), 3.81 (dd, 1H, *J* = 12.9, 3.5 Hz, H5'A), 3.96 (dd, 1H, *J* = 12.9, 2.9 Hz, H5'B), 4.27 (m, 1H, H3'), 4.28 (m, 1H, CHOH, H-malate), 4.39 (q, *J* = 3.4 Hz, 1H, H4'), 4.43 (t, 1H, *J* = 4.8 Hz, H2'), 6.17 (d, 1H, *J* = 4.4 Hz, H1'), 8.20 (t, 1H, 6.9 Hz, H5), 8.90 (d, 1H, *J* = 8.1 Hz, H4), 9.19 (d, 1H, *J* = 6.3

Hz, H6), 9.52 (s, 1H, H2). Impurities: 1 mol% nicotinamide; 0.45 mol% Et<sub>3</sub>N salt: 1.19 (t, 9H), 3.11 (q, 6H). Solvents: 9 mol% methanol: 3.25 (s, 3H).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): 40.0 (CH<sub>2</sub>, H-malate), 60.2 (C5'), 68.5 (CHOH, H-malate), 69.7 (C3'), 77.4 (C2'), 87.7 (C4'), 99.9 (C1'), 128.4 (C5), 133.9 (C3), 140.4 (C2), 142.6 (C6), 145.6 (C4), 165.7 (CONH<sub>2</sub>), 176.3 (COO, H-malate), 179.0 (COO, H-malate). Solvents: 48.9 (methanol).

**NR<sup>+</sup> DL-Hydrogen malate:** 4.52 g (67%) of a white, crystalline powder were obtained; Mp. 108-109 °C; IC: Residual bromide 2.30%.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): 2.54 (dd, 1H, *J* = 16.0, 8.1 Hz, CH<sub>2</sub>, H-malate), 2.72 (dd, 1H, *J* = 16.0, 4.3 Hz, CH<sub>2</sub>, H-malate), 3.82 (dd, 1H, *J* = 12.9, 3.5 Hz, H5'A), 3.96 (dd, 1H, *J* = 12.9, 2.9 Hz, H5'B), 4.27 (m, 1H, H3'), 4.28 (m, 1H, CHOH, H-malate), 4.40 (q, *J* = 3.4 Hz, 1H, H4'), 4.43 (t, 1H, *J* = 4.8 Hz, H2'), 6.17 (d, 1H, *J* = 4.4 Hz, H1'), 8.20 (t, 1H, 6.9 Hz, H5), 8.90 (d, 1H, *J* = 7.7 Hz, H4), 9.19 (d, 1H, *J* = 6.3 Hz, H6), 9.52 (s, 1H, H2). Impurities: < 1 mol% nicotinamide; 1.4 mol% Et<sub>3</sub>N salt: 1.19 (t, 9H), 3.11 (q, 6H). Solvents: 3.4 mol% methanol: 3.25 (s, 3H).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): 40.0 (CH<sub>2</sub>, H-malate), 60.2 (C5'), 68.5 (CHOH, H-malate), 69.7 (C3'), 77.4 (C2'), 87.7 (C4'), 99.9 (C1'), 128.4 (C5), 133.9 (C3), 140.4 (C2), 142.6 (C6), 145.6 (C4), 165.7 (CONH<sub>2</sub>), 176.3 (COO, H-malate), 179.0 (COO, H-malate). Impurity: 8.2, 46.6 (Et<sub>3</sub>N). Solvents: 48.9 (methanol).

**NR<sup>+</sup> D-Hydrogen tartrate:** 4.90 g (70%) of a white, crystalline powder were obtained; Mp. 124-126 °C; IC: Residual bromide 0.30%.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): 3.82 (dd, 1H, *J* = 12.9, 3.5 Hz, H5'A), 3.97 (dd, 1H, *J* = 12.9, 2.9 Hz, H5'B), 4.28 (t, 1H, *J* = 4.6 Hz, H3'), 4.38 – 4.46 (m, 2H, H2', H4'), 4.42 (s, 2H, 2 x CHOH, H-tartrate), 6.17 (d, 1H, *J* = 4.4 Hz, H1'), 8.20 (dd, 1H, *J* = 8.1, 6.2 Hz, H5), 8.90 (dt, 1H, *J* = 8.1, 1.4 Hz, H4), 9.19 (d, 1H, *J* = 6.2 Hz, H6), 9.52 (s, 1H, H2). Impurities: 1 mol% nicotinamide; 1.6 mol% Et<sub>3</sub>N salt: 1.19 (t, 9H), 3.11 (q, 6H). Solvents: 11 mol% methanol: 3.25 (s, 3H).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): 60.2 (C5'), 69.7 (C3'), 72.8 (2 x CHOH, H-tartrate), 77.4 (C2'), 87.7 (C4'), 99.9 (C1'), 128.4 (C5), 133.9 (C3), 140.4 (C2), 142.6 (C6), 145.6 (C4), 165.8 (CONH<sub>2</sub>), 176.3 (2 x COO, H-tartrate). Impurity: 8.2, 46.6 (Et<sub>3</sub>N). Solvents: 48.9 (methanol).

#### **NR<sup>+</sup> D-hydrogen tartrate monohydrate:**

2.0 g nicotinamide-β-D-ribofuranoside D-hydrogen tartrate prepared in the example above were dissolved in 9 ml water. 70 ml methanol were added to the colorless solution with stirring. After approximately one minute white crystals precipitated. One hour later the formed suspension was filtered. The residue was washed with methanol and dried in vacuo at 35 °C. 1.54 g (77 %) of a white crystalline powder of the monohydrate was obtained. Water content: 4.24 % (determined according to K. Fischer); Mp. 115-116 °C; IC: Residual bromide: < 0.01 %.

#### **Example 14: Preparation of nicotinamide-2,3,5-tri-O-acetyl-β-D-ribofuranoside triflate**

##### **Example 14a: according to our method**

11.55 g (94 mmol) of nicotinamide and 29.7 g (93 mmol, 1 eq) of β-D-ribofuranose 1,2,3,5-tetraacetate were dissolved upon stirring at room temperature in 750 mL of acetonitrile which has been dried over 3 Å molecular sieves. 18.2 mL (97 mmol, 1.03 eq) of trimethylsilyl triflate were added within 20 minutes. The yellow solution was stirred for 20 minutes. Subsequently, the solvent was removed in vacuo at 35 °C. The formed foam was dissolved in 300 mL of dichloromethane and 4.5 g of activated charcoal were added. The suspension was filtered and the filtrate was concentrated in vacuo.

Nicotinamide-2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranoside triflate was isolated as a yellow foam (49.5 g, quantitative yield).

$^1\text{H}$ -NMR (400 MHz,  $\text{D}_2\text{O}$ ): 2.10, 2.13, 2.17 (3 x s, 3 x 3H,  $\text{COCH}_3$ ), 4.53 (m, 2H,  $J = 2.5$  Hz,  $\text{H5}'$ ), 4.89 (m, 1H,  $\text{H4}'$ ), 5.46 (t, 1H,  $J = 5.5$  Hz,  $\text{H3}'$ ), 5.56 (dd, 1H,  $J = 5.5, 3.9$  Hz,  $\text{H2}'$ ), 6.59 (d, 1H,  $J = 3.9$  Hz,  $\text{H1}'$ ), 8.28 (t, 1H,  $J = 8.1$  Hz,  $\text{H5}$ ), 9.00 (d, 1H,  $J = 8.2$  Hz,  $\text{H4}$ ), 9.21 (d, 1H,  $J = 6.4$  Hz,  $\text{H6}$ ), 9.45 (s, 1H,  $\text{H2}$ ). Impurities: 4 mol% nicotinamide, 2 mol% D-ribose-tetraacetate.

$^{13}\text{C}$ -NMR (100 MHz,  $\text{D}_2\text{O}$ ): 19.8, 19.9, 20.2 (3 x  $\text{COCH}_3$ ), 62.6 ( $\text{C5}'$ ), 69.4 ( $\text{C3}'$ ), 76.4 ( $\text{C2}'$ ), 82.7 ( $\text{C4}'$ ), 97.3 ( $\text{C1}'$ ); 114.9 + 118.1 + 121.2 + 124.4 (q,  $\text{CF}_3$ ); 128.7 ( $\text{C5}$ ), 134.2 ( $\text{C3}$ ), 140.4 ( $\text{C2}$ ), 143.1 ( $\text{C6}$ ), 146.2 ( $\text{C4}$ ), 165.4 ( $\text{CONH}_2$ ), 172.3, 172.4, 173.3 (3x CO).

#### Example 14b: for comparison

The method was carried out as described by Tanimori using a high excess of trimethylsilyl triflate, wherein the product was isolated as described above. The obtained foam contained a complex mixture of compounds. 0.43 g (3.5 mmol, 1.11 eq) of nicotinamide and 1.00 g (3.14 mmol) of  $\beta$ -D-ribofuranose 1,2,3,5-tetraacetate were dissolved upon stirring at room temperature in 25 mL acetonitrile which has been dried over 3 Å molecular sieves. 5.00 mL (26.8 mmol, 8.5 eq) of trimethylsilyl triflate were added within 5 minutes. The yellow solution was stirred for an h. Subsequently, the solvent was removed in vacuo at 35 °C. The reddish-brown oil was dissolved in 11 mL of dichloromethane and 0.16 g of activated charcoal were added. The suspension was stirred for 15 min, filtered, and the filtrate was concentrated. 1.72 g of a yellow-brown oil were obtained.

$^1\text{H}$ -NMR (400 MHz,  $\text{D}_2\text{O}$ ): Complex mixture of compounds

#### Crystalline Salts through $\text{NR}^+$ -triacetate triflate

#### **Examples 15: Deacetylation of nicotinamide- $\beta$ -D-ribose-2,3,5-triacetate triflate for preparation of nicotinamide- $\beta$ -D-ribofuranoside L-hydrogen tartrate**

##### **Example 15a: Deacetylation using sulfuric acid and neutralization using triethylamine**

Preparation of a diluted sulfuric acid in methanol: 27 g of methanol were cooled down to 0 °C. 3.00 g (30.6 mmol) of a 96% sulfuric acid were added while stirring. 30 g of a 10% methanolic sulfuric acid were obtained.

Deacylation of nicotinamide-2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranoside triflate: 3.00 g (5.66 mmol) of nicotinamide-2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranoside triflate were dissolved in 15 mL of methanol while stirring. 5.55 g (5.66 mmol, 1 eq) of the above methanolic sulfuric acid were added. The resulting colorless solution was stirred at room temperature for three days. Control by thin-layer chromatography revealed complete deacylation and some nicotinamide impurities.

Conversion to nicotinamide- $\beta$ -D-ribose L-hydrogen tartrate after neutralization with triethylamine: 1.1 mL of triethylamine (7.89 mmol, 1.4 eq) were added to the above solution. 3.3 mL (5.61 mmol, 1 eq) of a 1.7 molar methanolic solution of triethylammonium L-hydrogen tartrate were added, wherein product immediately started precipitating. Subsequently, 0.40 g of L-tartaric acid (2.6 mmol, 0.46 eq) were added. The product suspension was stored for 12 h in a refrigerator. After filtration, the obtained solid was washed with methanol and ethanol and dried in vacuo at 30°C. Nicotinamide- $\beta$ -D-ribofuranoside L-hydrogen tartrate was isolated as a white crystalline powder (1.23 g, 54%). Mp. 127–128 °C.

$^1\text{H}$ -NMR (400 MHz,  $\text{D}_2\text{O}$ ): 3.81 (dd, 1H,  $J = 12.9, 3.6$  Hz,  $\text{H5}'\text{A}$ ), 3.95 (dd, 1H,  $J = 12.9, 2.9$  Hz,  $\text{H5}'\text{B}$ ),

4.25-4.29 (m, 1H, H3'), 4.36-4.45 (m, 2H, H4', H2'), 4.40 (s, 2H, 2 x CHOH, H-tartrate), 6.16 (d, 1H,  $J$  = 4.4 Hz, H1'), 8.19 (dd, 1H,  $J$  = 8.1, 6.3 Hz, H5), 8.89 (dt, 1H,  $J$  = 8.1, 1.5 Hz, H4), 9.18 (d, 1H,  $J$  = 6.3 Hz, H6), 9.51 (s, 1H, H2). Impurities: 2 mol% nicotinamide: 7.83 (m, 1H), 8.54 (m, 1H), 8.76 (d, 1H), 9.00 (s, 1H); 2.9 mol% Et<sub>3</sub>N salt: 1.18 (t, 9H), 3.10 (q, 6H). Solvents: 16 mol% methanol: 3.25 (s, 3H), 2 mol% ethanol.

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): 60.2 (C5'), 69.7 (C3'), 72.8 (2x CHOH, H-tartrate), 77.4 (C2'), 87.6 (C4'), 99.9 (C1'), 128.4 (C5), 133.9 (C3), 140.4 (C2), 142.6 (C6), 145.6 (C4), 165.8 (CONH<sub>2</sub>), 176.3 (2 x COO, H-tartrate). Impurities: 8.2, 46.6 (Et<sub>3</sub>N salt). Solvents: 48.9 (methanol).

#### **Example 15b: Deacetylation using HBr in glacial acetic acid and neutralization using triethylamine**

8.0 g (15 mmol) of nicotinamide-2,3,5-tri-*O*-acetyl-β-D-ribofuranoside triflate were dissolved in 32 mL of methanol while stirring. The solution was cooled down to 0–5°C. After addition of 5.2 mL (30 mmol, 2 eq) of HBr 33% in glacial acetic acid, the solution was kept stirring at room temperature. According to control by thin-layer chromatography, the product was deacylated after 48 h. The solution was divided into two halves.

Isolation of the formed intermediate bromide: One half of the solution (20.5 mL) was seeded with nicotinamide-β-D-ribofuranoside bromide and was stirred at RT. After about 30 min a suspension was formed. The suspension was filtered and the residue was washed with methanol and ethanol, and was subsequently dried in vacuo at 30 °C. Nicotinamide-β-D-ribofuranoside bromide was isolated as a white crystalline powder (0.62 g, 25%).

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): 3.87 (dd, 1H,  $J$  = 12.9, 3.6 Hz, H5'A), 4.01 (dd, 1H,  $J$  = 12.9, 2.9 Hz, H5'B), 4.30–4.35 (m, 1H, H3'), 4.44 (q, 1H,  $J$  = 3.4 Hz, H4'), 4.50 (t, 1H,  $J$  = 4.7 Hz, H2'), 6.22 (d, 1H,  $J$  = 4.4 Hz, H1'), 8.25 (dd, 1H,  $J$  = 8.1, 6.3 Hz, H5), 8.95 (dt, 1H,  $J$  = 8.1, 1.5 Hz, H4), 9.24 (d, 1H,  $J$  = 6.3 Hz, H6), 9.56 (s, 1H, H2). Impurities: 1 mol% nicotinamide (8.11 ppm).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): 60.2 (C5'), 69.8 (C3'), 77.4 (C2'), 87.7 (C4'), 100.0 (C1'), 128.5 (C5), 134.0 (C3), 140.4 (C2), 142.7 (C6), 145.7 (C4), 165.8 (CONH<sub>2</sub>). Solvents: 23.8 (iso-propanol).

Conversion to nicotinamide-β-D-ribose L-hydrogen tartrate after neutralization with triethylamine: 1.8 mL of triethylamine (12.9 mmol, 1.7 eq) were added to the other half of the solution, wherein HBr and acetic acid were partially neutralized. 4.4 mL (7.5 mmol, 1 eq) of a 1.7 M methanolic solution of triethylammonium L-hydrogen tartrate were added to the yellowish solution, wherein product started precipitating. After filtration and washing with methanol and ethanol, and drying in vacuo at 30 °C, nicotinamide-β-D-ribofuranoside L-hydrogen tartrate was isolated as a white crystalline powder (1.62 g, 53%). Mp. 127–128 °C.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): Analogous to Example 15a. Impurities: 1 mol% nicotinamide; 3.7 mol% Et<sub>3</sub>N salt. Solvents: 12.5 mol% methanol.

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): Analogous to Example 15a.

#### **Example 15c: Deacetylation using hydrochloric acid and neutralization using triethylamine**

8.00 g (15.1 mmol) of nicotinamide-2,3,5-tri-*O*-acetyl-β-D-ribofuranoside triflate were dissolved in 32 mL of methanol while stirring. 5.5 mL (31 mmol, 2 eq) of a 5.6 M solution of hydrogen chloride in ethanol were added while cooling. The resulting colorless solution was stirred at RT overnight. Control by thin-layer chromatography revealed complete deacetylation and some nicotinamide impurities. The solution was divided into two halves.

Isolation of the formed intermediate chloride: One half of the solution (20.5 mL) was seeded with



nicotinamide- $\beta$ -D-ribofuranoside chloride and stirred at room temperature. After about 2 h, a very thin suspension was formed, which was stored overnight in the refrigerator. The thin suspension was filtered, the residue was washed with ethanol and subsequently dried in vacuo at 30 °C. Only 0.05 g (2%) of a white crystalline powder of nicotinamide-beta-D-ribofuranoside chloride were obtained. Mp. 104 °C.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): 3.85 (dd, 1H, *J* = 12.9, 3.5 Hz, H5'A), 3.99 (dd, 1H, *J* = 12.9, 2.9 Hz, H5'B), 4.27–4.35 (m, 1H, H3'), 4.42 (q, 1H, *J* = 3.5 Hz, H4'), 4.47 (t, 1H, *J* = 4.7 Hz, H2'), 6.20 (d, 1H, *J* = 4.5 Hz, H1'), 8.24 (d, 1H, *J* = 6.9 Hz, H5), 8.93 (d, 1H, *J* = 8.1, H4), 9.22 (d, 1H, *J* = 6.3 Hz, H6), 9.54 (s, 1H, H2). Impurities: 3 mol% nicotinamide (8.07 ppm).

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): 60.2 (C5'), 69.8 (C3'), 77.4 (C2'), 87.7 (C4'), 100.0 (C1'), 128.5 (C5), 134.0 (C3), 140.4 (C2), 142.7 (C6), 145.7 (C4), 165.8 (CONH<sub>2</sub>).

Conversion to nicotinamide- $\beta$ -D-ribose L-hydrogen tartrate after neutralization with triethylamine: 1.6 mL of triethylamine (11.5 mmol, 1.5 eq) were added dropwise to the other half of the above solution. 4.4 mL (7.5 mmol, 1 eq) of a 1.7 molar methanolic solution of triethylammonium L-hydrogen tartrate were added to the almost colorless solution, wherein product started precipitating. The suspension was stirred for a few hours and then stored for 16 h in a refrigerator. After filtration, the obtained solid was washed with methanol and ethanol and dried in vacuo at 30 °C. 1.82 g (60%) of a white crystalline powder of nicotinamide-beta-D-ribofuranoside L-hydrogen tartrate were obtained. Mp. 124–125 °C.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): Analogous to Example 15a. Impurities: < 1 mol% nicotinamide; 3.8 mol% Et<sub>3</sub>N salt. Solvents: 8.3 mol% methanol.

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): Analogous to Example 15a.

#### **Example 15d: Deacetylation using triethylamine**

Deacylation of nicotinamide-D-ribose-2,3,5-triacetate triflate: 3.00 g (5.66 mmol) of the triflate were dissolved in 18 mL methanol while stirring. 0.8 mL (5.7 mmol, 1 eq) of triethylamine were added to the solution cooled down to 0 °C. After stirring for 4 days at 0–5°C, thin-layer control showed complete conversion.

Conversion to nicotinamide- $\beta$ -D-ribose L-hydrogen tartrate: The brown-orange solution obtained in the step above was warmed to RT. Subsequently, 0.86 g (5.7 mmol, 1 eq) of L-tartaric acid were added, and a suspension was formed. The product suspension was cooled down to 0 °C and stirred. After storage in a refrigerator for 12 h, the suspension was filtered, the obtained solid washed with 5 mL isopropanol and dried in vacuo at 30 °C. 1.44 g (63%) of a brownish-yellow crystalline powder were obtained. Mp. 127 °C.

<sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): Analogous to Example 15a. Impurities: 2 mol% nicotinamide; 1.9 mol% Et<sub>3</sub>N salt. Solvents: 13.3 mol% methanol, 2.8 mol% isopropanol.

<sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): Analogous to Example 15a.

#### **Examples 16: Deacetylation of nicotinamide- $\beta$ -D-ribose-2,3,5-triacetate triflate for preparation of nicotinamide- $\beta$ -D-ribofuranoside L-hydrogen malate**

##### **Example 16a: Deacetylation using sulfuric acid and neutralization using triethylamine**

Preparation of a diluted sulfuric acid in methanol: 27 g of methanol were cooled down to 0 °C. 3.00 g (30.6 mmol) of a 96% sulfuric acid were added while stirring. 30 g of a 10% methanolic sulfuric

acid were obtained.

Deacylation of nicotinamide-2,3,5-tri-O-acetyl- $\beta$ -D-ribofuranoside triflate: 8.00 g (15.1 mmol) of nicotinamide-2,3,5-tri-O-acetyl- $\beta$ -D-ribofuranoside triflate were dissolved in 10 mL of methanol while stirring. 15.6 g (15.9 mmol, 1.05 eq) of the above methanolic sulfuric acid were added. The resulting colorless solution was stirred at RT for 16 h. Control by thin-layer chromatography revealed complete deacylation and some nicotinamide impurities.

Conversion to nicotinamide- $\beta$ -D-ribose L-hydrogen malate after neutralization with triethylamine: 3.0 mL (21.5 mmol, 1.4 eq) of triethylamine were added dropwise to the above solution. 2.03 g (15.1 mmol, 1 eq) of L-malic acid were added, followed by additional 2.5 mL (18 mmol, 1.2 eq) of triethylamine. The product soon started precipitating. The suspension was stirred for a few h and then stored for 12 h in a refrigerator. After filtration, the obtained solid was washed with methanol and ethanol and dried in vacuo at 30 °C. 2.15 g (36.7%) of a white crystalline powder were obtained. Mp. 109–110°C.

$^1\text{H-NMR}$  (400 MHz,  $\text{D}_2\text{O}$ ): 2.52 (dd, 1H,  $J = 16.0, 8.1$  Hz,  $\text{CH}_2$ , H-malate), 2.71 (dd, 1H,  $J = 16.0, 4.2$  Hz,  $\text{CH}_2$ , H-malate), 3.81 (dd, 1H,  $J = 12.9, 3.5$  Hz,  $\text{H5}'\text{A}$ ), 3.92–4.00 (m,  $\text{H5}'\text{B}$ ), 4.24–4.31 (m, 1H,  $\text{H3}'$  and 1H,  $\text{CHOH}$ , H-malate), 4.39 (q, 1H,  $J = 3.4$  Hz,  $\text{H4}'$ ), 4.43 (t, 1H,  $J = 4.7$  Hz,  $\text{H2}'$ ), 6.17 (d, 1H,  $J = 4.5$  Hz,  $\text{H1}'$ ), 8.20 (dd, 1H,  $J = 8.0, 6.3$  Hz,  $\text{H5}$ ), 8.90 (d, 1H,  $J = 7.6$  Hz,  $\text{H4}$ ), 9.19 (d, 1H,  $J = 6.3$  Hz,  $\text{H6}$ ), 9.51 (s, 1H,  $\text{H2}$ ). Impurities: < 1 mol% nicotinamide; 0.9 mol%  $\text{Et}_3\text{N}$  salt. Solvents: 3.7 mol% methanol.  $^{13}\text{C-NMR}$  (100 MHz,  $\text{D}_2\text{O}$ ): 40.1 ( $\text{CH}_2$ , H-malate), 60.2 ( $\text{C5}'$ ), 68.5 ( $\text{CHOH}$ , H-malate), 69.7 ( $\text{C3}'$ ), 77.4 ( $\text{C2}'$ ), 87.7 ( $\text{C4}'$ ), 99.9 ( $\text{C1}'$ ), 128.4 ( $\text{C5}$ ), 133.9 ( $\text{C3}$ ), 140.4 ( $\text{C2}$ ), 142.6 ( $\text{C6}$ ), 145.7 ( $\text{C4}$ ), 165.8 ( $\text{CONH}_2$ ), 176.3 ( $\text{COO}$ , H-malate), 179.1 ( $\text{COO}$ , H-malate).

#### **Example 16b: Deacetylation using HBr in glacial acetic acid, neutralization using tributylamine**

Deacylation of nicotinamide-2,3,5-tri-O-acetyl-D-ribofuranoside triflate: 2.00 g (3.8 mmol) of the triflate were dissolved in 8 mL of methanol while stirring. The solution was cooled down to 0–5°C. After addition of HBr 33% in glacial acetic acid (1.33 mL, 7.6 mmol, 2 eq), the green-yellowish solution was stirred at RT. After two days no educt could be determined in the solution by thin-layer chromatography.

Conversion to nicotinamide- $\beta$ -D-ribofuranoside L-hydrogen malate after neutralization with tributylamine: 1.3 mL (5.45 mmol, 1.43 eq) of tributylamine were added to the above solution. After addition of 0.6 mL of water, any precipitated material was completely dissolved. 0.51 g (3.8 mmol, 1 eq) of L-malic acid were added to the brown-yellowish solution. After addition of further 0.9 mL (3.8 mmol, 1 eq) of tributylamine, the deacetylated product started crystallizing. It was filtered off, washed with methanol and dried in vacuo at 30 °C. 0.48 g (33 %) of nicotinamide- $\beta$ -D-ribofuranoside L-hydrogen malate were obtained. Mp. 115–116°C.

$^1\text{H-NMR}$  (400 MHz,  $\text{D}_2\text{O}$ ): 2.55 (dd, 1H,  $J = 16.0, 8.1$  Hz,  $\text{CH}_2$ , H-malate), 2.74 (dd, 1H,  $J = 16.0, 4.3$  Hz,  $\text{CH}_2$ , H-malate), 3.83 (dd, 1H,  $J = 12.9, 3.5$  Hz,  $\text{H5}'\text{A}$ ), 3.98 (dd, 1H,  $J = 12.9, 2.9$  Hz,  $\text{H5}'\text{B}$ ), 4.28 (m, 1H,  $\text{H3}'$ ), 4.30 (m, 1H,  $\text{CHOH}$ , H-malate), 4.39–4.42 (m, 1H,  $\text{H4}'$ ), 4.44 (t, 1H,  $J = 4.8$  Hz,  $\text{H2}'$ ), 6.18 (d, 1H,  $J = 4.5$  Hz,  $\text{H1}'$ ), 8.21 (dd, 1H,  $J = 8.1, 6.3$  Hz,  $\text{H5}$ ), 8.91 (d, 1H,  $J = 7.8$  Hz,  $\text{H4}$ ), 9.20 (d, 1H,  $J = 6.3$  Hz,  $\text{H6}$ ), 9.53 (s, 1H,  $\text{H2}$ ). Impurities: < 1 mol% nicotinamide; 0.35 mol%  $\text{Bu}_3\text{N}$  salt: 0.85 (t, 9H), 1.29 (m, 6H), 1.59 (m, 6H), 3.05 (q, 6H); solvents: 2.3 mol% methanol: 3.27 (s, 3H).

$^{13}\text{C-NMR}$  (100 MHz,  $\text{D}_2\text{O}$ ): 40.0 ( $\text{CH}_2$ , H-malate), 60.2 ( $\text{C5}'$ ), 68.5 ( $\text{CHOH}$ , H-malate), 69.8 ( $\text{C3}'$ ), 77.4 ( $\text{C2}'$ ), 87.7 ( $\text{C4}'$ ), 99.9 ( $\text{C1}'$ ), 128.4 ( $\text{C5}$ ), 133.9 ( $\text{C3}$ ), 140.4 ( $\text{C2}$ ), 142.6 ( $\text{C6}$ ), 145.6 ( $\text{C4}$ ), 165.8 ( $\text{CONH}_2$ ), 176.3 ( $\text{COO}$ , H-malate), 179.0 ( $\text{COO}$ , H-malate).

#### **Example 16c: Deacetylation using hydrochloric acid and neutralization using triethylamine**

Deacylation of nicotinamide-2,3,5-tri-O-acetyl- $\beta$ -D-ribofuranoside triflate: 8.00 g (15.1 mmol) of nicotinamide-2,3,5-tri-O-acetyl- $\beta$ -D-ribofuranoside triflate were dissolved in 32 mL of methanol while stirring. 4.6 mL (25.8 mmol, 1.7 eq) of a 5.6 M solution of hydrogen chloride in ethanol were added while cooling. The resulting colorless solution was stirred at RT overnight. Control by thin-layer chromatography revealed complete deacetylation and some nicotinamide impurities.

Conversion to nicotinamide- $\beta$ -D-ribose L-hydrogen malate after neutralization with triethylamine: 3.0 mL (21.5 mmol, 1.4 eq) of triethylamine were added dropwise to the above solution. 2.03 g (15.1 mmol, 1 eq) of L-malic acid were added, followed by additional 1.55 mL (11.1 mmol, 0.74 eq) of triethylamine. The product soon started precipitating. The suspension was stirred for a few h and then stored for 16 h in a refrigerator. After filtration, the obtained solid was washed with methanol and ethanol and dried in vacuo at 30 °C. 2.54 g (43.3%) of a white crystalline powder were obtained. Mp. 112–113 °C.

$^1\text{H}$ -NMR (400 MHz,  $\text{D}_2\text{O}$ ): Analogous to **Example 16a**. Impurities: < 1 mol% nicotinamide; 0.5 mol%  $\text{Et}_3\text{N}$  salt. Solvents: 3.7 mol% methanol.

$^{13}\text{C}$ -NMR (100 MHz,  $\text{D}_2\text{O}$ ): Analogous to **Example 16a**.

#### **Example 16d: Deacetylation using triethylamine**

Deacylation of nicotinamide-D-ribose-2,3,5-triacetate triflate: 3.00 g (5.66 mmol) of the triflate were dissolved in 18 mL of methanol while stirring. 0.8 mL of triethylamine (5.7 mmol, 1 eq) were added to the solution cooled down to 0 °C. After stirring for 4 days at 0–5 °C, thin-layer control showed complete conversion.

Conversion to nicotinamide- $\beta$ -D-ribose L-hydrogen malate: The brown-orange solution obtained in the step above was warmed to RT. Subsequently, 0.80 g (5.9 mmol, 1.04 eq) of L-malic acid were added. Product started precipitating after a few minutes. The product suspension was cooled down to 0 °C and stirred. After storage in a refrigerator for 12 h, the suspension was filtered, the obtained solid washed with methanol and ethanol and dried in vacuo at 30 °C. 0.95 g (43 %) of a yellow-beige crystalline powder were obtained. Mp. 111–112 °C

$^1\text{H}$ -NMR (400 MHz,  $\text{D}_2\text{O}$ ): Analogous to **Example 16a**. Impurities: < 1 mol% nicotinamide; 1 mol%  $\text{Et}_3\text{N}$  salt. Solvents: 11 mol% methanol.

$^{13}\text{C}$ -NMR (100 MHz,  $\text{D}_2\text{O}$ ): Analogous to **Example 16a**.

#### **Example 17: Preparation of nicotinamide-2,3,5-tri-O-acetyl- $\beta$ -D-ribofuranoside iodide**

6.00 g (49 mmol, 1.04 eq) of nicotinamide and 14.9 g (47 mmol) of  $\beta$ -D-ribofuranose-1,2,3,5-tetraacetate were suspended upon stirring at RT in 190 mL of acetonitrile which has been dried over 3 Å molecular sieves. The suspension was warmed to 35 °C while most of the solids dissolved. 7.0 mL (49 mmol, 1.04 eq) of trimethylsilyl iodide were added within 20 minutes and the yellow suspension was stirred for a further two hours at 35 °C. Subsequently, the internal temperature was kept at 40 °C and 45 °C for one hour each. The solvent was removed in vacuo at 35 °C. The formed foam was dissolved in 100 mL of dichloromethane and 1.2 g of activated charcoal were added. The suspension was filtered, and the filtrate was concentrated in vacuo. Nicotinamide-2,3,5-tri-O-acetyl- $\beta$ -D-ribofuranoside iodide was isolated as a deep yellow foam (22 g, 93%).

$^1\text{H}$ -NMR (400 MHz,  $\text{D}_2\text{O}$ ): 2.03, 2.06, 2.10 (3x s, 3 x 3H,  $\text{COCH}_3$ ), 4.43–4.50 (m, 2H,  $\text{H}_5'$ ), 4.81–4.86 (m, 1H,  $\text{H}_4'$ ), 5.40 (t, 1H,  $J = 5.4$  Hz,  $\text{H}_3'$ ), 5.49–5.55 (m, 1H,  $\text{H}_2'$ ), 6.55 (d, 1H,  $J = 3.9$  Hz,  $\text{H}_1'$ ), 8.24 (dd,

$^1\text{H}$ ,  $J = 8.1, 6.3 \text{ Hz}$ , H5), 9.16 (d, 1H, H4), 9.18 (d, 1H, H6), 9.38 (s, 1H, H2). Impurities: 24 mol% ribose tetraacetate, 16 mol% alpha-anomer, 3 mol% nicotinamide.

$^{13}\text{C}$ -NMR (100 MHz,  $\text{D}_2\text{O}$ ): 20.0, 20.1, 20.4 (3  $\times$   $\text{COCH}_3$ ), 62.6 ( $\text{C}5'$ ), 69.3 ( $\text{C}3'$ ), 76.1 ( $\text{C}2'$ ), 82.5 ( $\text{C}4'$ ), 97.2 ( $\text{C}1'$ ), 128.8 ( $\text{C}5$ ), 134.1 ( $\text{C}3$ ), 140.4 ( $\text{C}2$ ), 143.1 ( $\text{C}6$ ), 146.2 ( $\text{C}4$ ), 165.1 ( $\text{CONH}_2$ ), 172.0, 172.1, 173.0 (3  $\times$   $\text{CO}$ ).

### **Example 18: Deacetylation of nicotinamide- $\beta$ -D-ribose-2,3,5-triacetate iodide**

#### **Deacetylation using sulfuric acid and neutralization using triethylamine**

Preparation of a diluted sulfuric acid in methanol: 10 mL of methanol were cooled down to 0 °C. 1.20 mL (21.6 mmol) of a 96% sulfuric acid were added while stirring. The methanolic sulfuric acid was used in the deacetylation below.

Deacylation of nicotinamide-2,3,5-tri- $O$ -acetyl- $\beta$ -D-ribofuranoside iodide: 11.0 g (21.6 mmol) of nicotinamide-2,3,5-tri- $O$ -acetyl- $\beta$ -D-ribofuranoside iodide were dissolved in 33 mL of methanol while stirring. The above prepared methanolic sulfuric acid was added. The resulting orange-brown solution was stirred at room temperature for 24 h. Control by thin-layer chromatography revealed complete deacylation and some impurities. 3.5 mL (25.1 mmol, 1.16 eq) of triethylamine were added. The solution was divided into two halves.

Conversion to nicotinamide- $\beta$ -D-ribose L-hydrogen tartrate after neutralization with triethylamine: To one half of the above solution 1.65 g (11 mmol, 1.02 eq) of L-tartaric acid were added, followed by further 1.6 mL (11.5 mmol, 1.06 eq) of triethylamine. Product started precipitating almost immediately. The product suspension was stirred one h at RT, two h in an ice-bath and stored for 12 h in a refrigerator. After filtration, the obtained solid was washed with methanol and dried in vacuo at 30 °C. Nicotinamide- $\beta$ -D-ribofuranoside L-hydrogen tartrate was isolated as an almost white crystalline powder (2.10 g, 48%). Mp. 125.5–126°C.

$^1\text{H}$ -NMR (400 MHz,  $\text{D}_2\text{O}$ ): Analogous to **Example 15a**. Impurities: 1 mol% nicotinamide; 3.8 mol%  $\text{Et}_3\text{N}$  salt. Solvents: 18.2 mol% methanol.

$^{13}\text{C}$ -NMR (100 MHz,  $\text{D}_2\text{O}$ ): Analogous to **Example 15a**.

Conversion to nicotinamide- $\beta$ -D-ribose L-hydrogen malate after neutralization with triethylamine: 1.45 g of L-malic acid (10.8 mmol, 1 eq) were added to the other half of the above solution, followed by further 1.1 mL (7.9 mmol, 0.73 eq) of triethylamine. The solution was seeded and the product started precipitating a few min later. The product suspension was stirred one h at RT, two h in an ice-bath, then stored for 12 h in a refrigerator. After filtration, the obtained solid was washed with methanol and ethanol and dried in vacuo at 30 °C. Nicotinamide- $\beta$ -D-ribofuranoside L-hydrogen malate was isolated as an almost white crystalline solid (1.37 g, 32.7%). Mp. 114–115°C.

$^1\text{H}$ -NMR (400 MHz,  $\text{D}_2\text{O}$ ): Analogous to **Example 16a**. Impurities: 0.5 mol% nicotinamide; 0.5 mol%  $\text{Et}_3\text{N}$  salt. Solvents: 2.4 mol% methanol, 0.4 mol% ethanol.

$^{13}\text{C}$ -NMR (100 MHz,  $\text{D}_2\text{O}$ ): Analogous to **Example 16a**.

### Section S3: Solubility of NR<sup>+</sup> crystalline salts

Table S3: Solubilities (in mL solvent per g of solute) of the stereoisomeric crystalline NR<sup>+</sup> salts and the halogenides in methanol and in aqueous solutions.

NR <sup>+</sup> salts	Solubility in MeOH	Solubility in MeOH / H <sub>2</sub> O 4:1	Solubility in Water
D-Hydrogen malate	1300	220	3.3
L-Hydrogen malate	500	50	1.05
DL-Hydrogen malate	750	120	2.3
D-Hydrogen tartrate	400	40	4.2
L-Hydrogen tartrate	3800	410	5.3
DL-Hydrogen tartrate	2600	300	3.8
Bromide	50	6	0.5
Chloride	40	5	0.55

### Section S4: Single Crystal Growth and Structural Determination of Nicotinamide riboside derivatives by X-Ray Diffraction

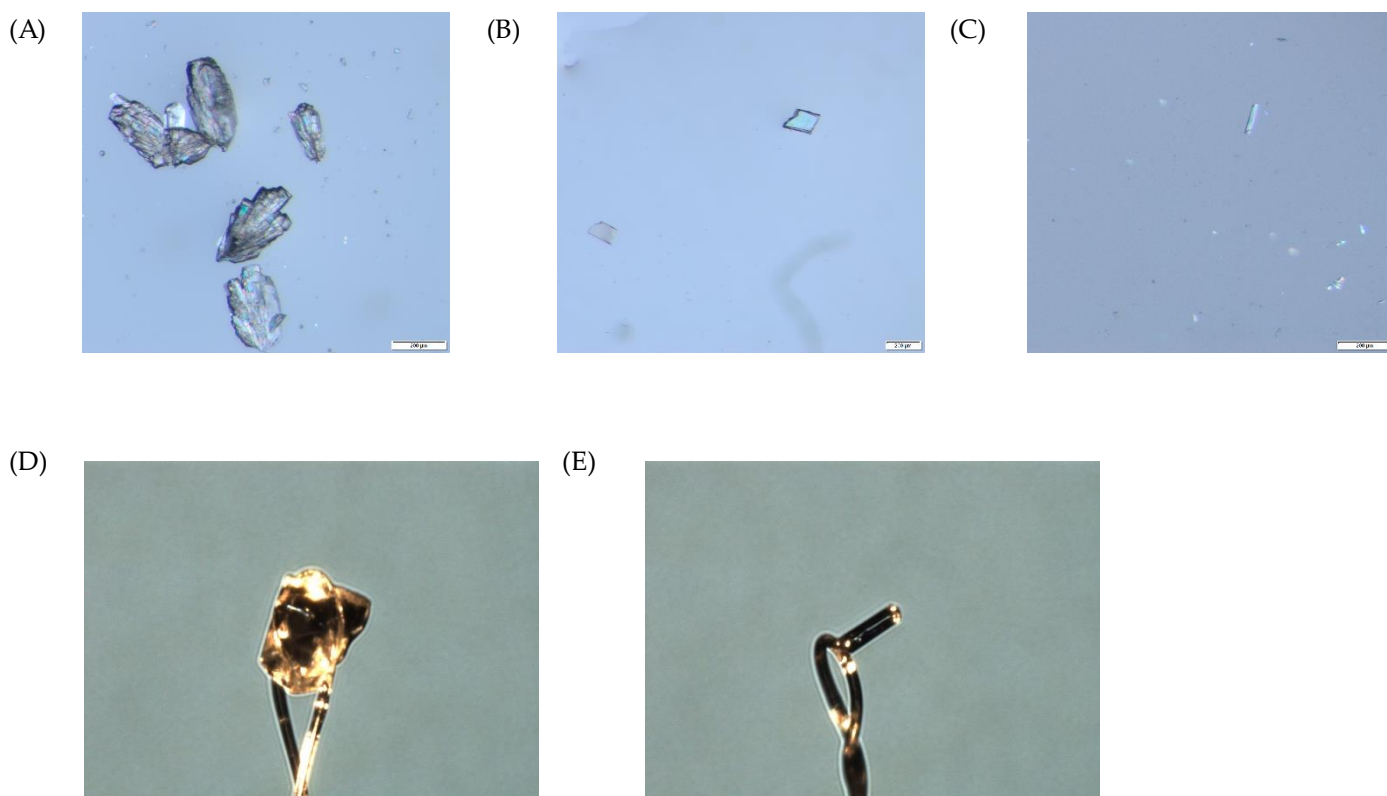


Figure S1: Photos of the grown crystals of **11a** (anhydrate of **11**) (A), **11b** (monohydrate of **11**) (B), **12** (C), **13** (D) and **14** (E).

Table S4: Summary of Crystal Data and Structure Refinement of the Salts **11a**, **11b**, **12**, **13**, and **124**.

	<b>11a</b> (anhydrate)	<b>11b</b> (hydrate)	<b>12</b>	<b>13</b>	<b>14</b>
Empirical formula	C <sub>15</sub> H <sub>20</sub> N <sub>2</sub> O <sub>11</sub>	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O <sub>12</sub>	C <sub>15</sub> H <sub>20</sub> N <sub>2</sub> O <sub>11</sub>	C <sub>15</sub> H <sub>20</sub> N <sub>2</sub> O <sub>10</sub>	C <sub>15</sub> H <sub>20</sub> N <sub>2</sub> O <sub>10</sub>
Formula weight	404.33	422.34	404.33	388.33	388.33
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Orthorhombic
Space group	P2 <sub>1</sub>	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	P2 <sub>1</sub>	P2 <sub>1</sub>	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
a [Å]	7.52820(10)	7.71190(10)	7.64990(12)	7.66800(10)	7.35565(8)
b [Å]	7.70690(10)	14.56510(10)	13.8774(2)	8.21630(10)	7.82204(8)
c [Å]	14.33700(10)	15.1856(2)	7.80215(13)	13.4615(2)	28.1002(2)
α [°]	90	90	90	90	90
β [°]	96.8240(10)	90	96.2221(15)	96.4630(10)	90
γ [°]	90	90	90	90	90
Volume [Å <sup>3</sup> ]	825.927(16)	1705.72(3)	823.40(2)	842.72(2)	1616.78(3)
Z	2	4	2	2	4
Density (calculated) [Mg/m <sup>3</sup> ]	1.626	1.645	1.631	1.530	1.595
Temperature [K]	160.00(10)	160.00(10)	159.99(10)	160.00(10)	160.00(10)
Wavelength [Å]	1.54184	1.54184	0.71073	0.71073	1.54184
Absorption coefficient [mm <sup>-1</sup> ]	1.223	1.256	0.141	0.130	1.175
F(000)	424	888	424	408	816
Crystal size [mm <sup>3</sup> ]	0.111 × 0.055 × 0.022	0.127 × 0.025 × 0.02	0.226 × 0.073 × 0.065	0.32 × 0.28 × 0.204	0.215 × 0.051 × 0.045
Crystal description	colorless plate	colorless needle	colorless block	colorless block	colorless needle
Theta range for data collection [°]	3.104 to 79.576	4.206 to 79.535	2.626 to 37.874	2.673 to 37.797	5.872 to 79.555
Index ranges	-6 ≤ h ≤ 9 -9 ≤ k ≤ 9 -18 ≤ l ≤ 18	-9 ≤ h ≤ 9 -18 ≤ k ≤ 18 -18 ≤ l ≤ 15	-13 ≤ h ≤ 11 -23 ≤ k ≤ 23 -13 ≤ l ≤ 13	-12 ≤ h ≤ 13 -14 ≤ k ≤ 14 -22 ≤ l ≤ 23	-9 ≤ h ≤ 9 -8 ≤ k ≤ 9 -35 ≤ l ≤ 28
Reflections collected	14426	18041	34397	34851	17769
Independent reflections	3442 [R(int) = 0.0369]	3683 [R(int) = 0.0273]	8442 [R(int) = 0.0249]	8567 [R(int) = 0.0305]	3505 [R(int) = 0.0324]
Reflections observed	3367	3589	7909	8252	3423
Criterion for observation	I > 2 σ(I)	I > 2 σ(I)	I > 2 σ(I)	I > 2 σ(I)	I > 2 σ(I)
Completeness to theta	97.6 % to 67.684°	100.0 % to 67.684°	100.0 % to 25.242°	99.9 % to 25.242°	99.9 % to 67.684°
Absorption correction	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian
Max. and min. transmission	1.000 and 0.854	1.000 and 0.793	1.000 and 0.807	1.000 and 0.420	1.000 and 0.632
Data / restraints / parameters	3442 / 1 / 260	3683 / 0 / 275	8442 / 1 / 259	8567 / 1 / 249	3505 / 0 / 250
Goodness-of-fit on F <sup>2</sup>	1.070	1.054	1.074	1.039	1.084
Final R indices [I > 2 σ(I)]	R1 = 0.0307, wR2 = 0.0803	R1 = 0.0244, wR2 = 0.0638	R1 = 0.0322, wR2 = 0.0870	R1 = 0.0297, wR2 = 0.0828	R1 = 0.0294, wR2 = 0.0789
R indices (all data)	R1 = 0.0318, wR2 = 0.0841	R1 = 0.0253, wR2 = 0.0641	R1 = 0.0350, wR2 = 0.0887	R1 = 0.0309, wR2 = 0.0835	R1 = 0.0304, wR2 = 0.0800
Absolute structure parameter	0.04(7)	0.02(5)	0.01(14)	0.03(14)	0.01(6)
Extinction coefficient	0.0030(8)	0.0011(2)	n/a	n/a	0.0014(3)
Largest diff. peak and hole [e.Å <sup>-3</sup> ]	0.280 and -0.195	0.202 and -0.175	0.445 and -0.222	0.497 and -0.230	0.426 and -0.210

### Discussion of the hydrogen bonding network of **11a**

There are several direct hydrogen bonds and other chain motifs in the structure. The nitrogen of the amide group forms hydrogen bonds with the oxygen atoms of hydroxyl groups on a neighboring hydrogen tartrate molecule (N2-H2B O12 (+x, +y, 1+z): 2.779(3) Å, N2-H2B O14 ((+x, +y, 1+z): 3.020(3) Å). O2, O3, and O5 of hydroxyl groups on the riboside form individual hydrogen bonds with the carbonyl of the hydrogen tartrate, and two neighboring riboside units, respectively (O2-H2 O13: 2.616(2) Å), O3-H O5 (+x, 1+y, +z): 2.718(3) Å), (O5-H5 O2 (-x, -0.5+y, 1-z): 2.772(3) Å). The donor O3 is also the start of a seven membered chain ending with the acceptor atom. The donor O5 is also the start of a six membered chain which ends at the acceptor O2. Two oxygen atoms of hydroxyl groups on the same hydrogen tartrate form hydrogen bonds with the carbonyl amide of a different neighboring riboside (O14-H14 O1 (-x, -0.5+y, 1-z): 2.805(3) Å, O15-H15 O1 (1-x, -0.5 + y, 1-z): 2.823(3) Å). An additional hydroxyl oxygen of the riboside forms a hydrogen bond with an oxygen of a neighboring hydrogen tartrate (O17-H17 O12 (-x, -1+y, +z): 2.473(3) Å). From this donor atom, O17, a seven membered chain motif propagates to the acceptor O12.

### Discussion of the hydrogen bonding network of **11b**

There are various hydrogen bonding motifs in the structure. The hydroxyl groups of the riboside form hydrogen bonds with oxygen atoms of the neighboring hydrogen tartrate and O2 forms a hydrogen bond with the oxygen of the water molecule (O3-H3 O13 (1 + x, + y, + z): 2.8723(18) Å, O5-H5 O2 (1 + x, + y, + z): 2.7760(17) Å, O2-H2 O6: 2.6299(18) Å). From the donor atom O5, there begins a seven membered chain ending with the acceptor O2. The oxygen of the water molecule forms additional hydrogen bonds with the carbonyl oxygen of the hydrogen tartrate molecule and a hydroxyl group of a neighboring hydrogen tartrate molecule (O6-H6A O13: 2.7584(19) Å, O6-H6B O17 (1 + x, + y, + z): 2.8330(19) Å). The hydroxy groups of hydrogen tartrate molecule at O14, O15, and O17 form hydrogen bonds with the oxygen of a neighboring riboside sugar, the amide group, and neighboring hydrogen tartrate molecule, respectively (O14-H14 O5 (1 - x, -0.5 + y, 0.5 - z): 2.7797(19) Å, O15-H15 O1 (-1.5 + x, 0.5 - y, 1-z): 2.9135(19) Å, O17-H17 O12 (-1 + x, + y, + z) 2.4916(17) Å). At O17 a seven membered chain begins and extends to the acceptor atom O12. Further there is an intramolecular hydrogen bond from O15 of the hydrogen tartrate hydroxyl group to the carbonyl oxygen (O15-H15 O16: 2.7083(18) Å).

### Discussion of the hydrogen bonding network of **12**

There are various discrete hydrogen bonds present. The amide group forms hydrogen bonds with a carbonyl and a hydroxyl oxygen of two neighboring hydrogen tartrate molecules (N2-H2A O16 (-1 - x, -0.5 + y, -z): 2.9950(13) Å, N2-H2B O15 (-x, -0.5 + y, -z): 2.9925(13) Å). There are hydrogen bonds between different hydroxyl group of the riboside with two oxygens of the hydrogen tartrate molecule in the same asymmetric unit (O2-H2 O12: 2.7951(12) Å, O2-H2 O14: 2.8782(13) Å). Other hydroxyl oxygens of the riboside form hydrogen bonds with a carbonyl of a neighboring hydrogen tartrate and with a hydroxyl oxygen of a neighboring riboside (O3-H3 O13 (-x, 0.5+y, -z): 2.6638(12) Å, O5-H5 O2 (1 + x, + y, + z): 2.7162(13) Å). At O5 of the riboside a seven membered chain motif begins, ending at the acceptor atom O2. The hydrogen tartrate hydroxyl groups form hydrogen bonds from to the riboside in the same asymmetric unit, a neighboring riboside and a neighboring hydrogen tartrate molecule (O14-H14 O1: 2.8011(13) Å, O15-H15 O5 (-1 + x, + y, 1 + z): 2.6544(13) Å, and O17-H17 O12 (-1 + x, + y, + z): 2.5755(11) Å). A fourteen membered ring is formed from the riboside by the proton of O2 to O14 of the hydrogen tartrate, and the proton of O14 forms a hydrogen bond with O1, in the same asymmetric unit. Additionally, at the donor atom, O17, there begins a seven membered chain motif ending with the acceptor O12.

### Discussion of the hydrogen bonding network of **13**

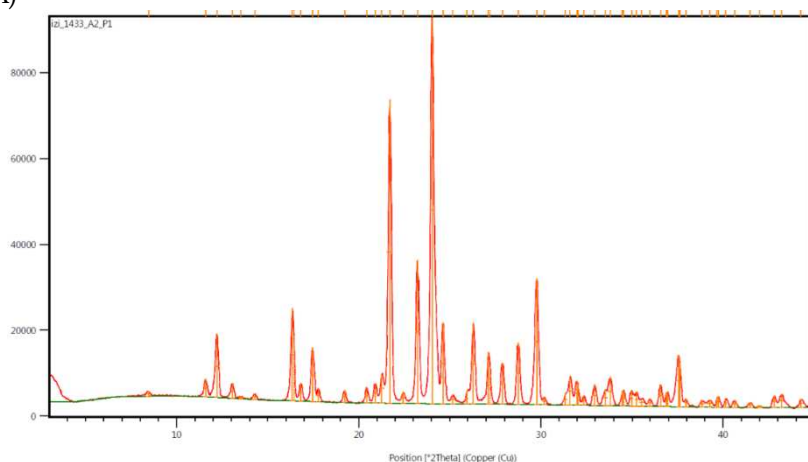
The nitrogen of the amide group forms hydrogen bonds with a deprotonated oxygen and a carbonyl of two neighboring hydrogen malate molecules (N2-H2A O14 (-1 + x, +y, 1 + z): 3.0865(12) Å, N2-H2B O13 (+ x, + y,

1+z): 2.8994(11) Å. Two hydroxyl oxygens, O2, and O3, of the riboside form hydrogen bonds with oxygen atoms of neighboring hydrogen malate (O2-H2 O15 (-1 +x, +y, +z): 2.74313(11) Å, O3-H3 O12: 2.6532(11) Å). A third hydroxyl oxygen of the riboside forms a hydrogen bond with the oxygen of a neighboring amide (O5-H5 O1 (1 +x, +y, +z): 2.7685(11) Å). This hydrogen bond beginning with the donor O5 propagates through a chain of eleven atoms and ends with the acceptor atom, O1. Another hydroxyl oxygen of the riboside forms a hydrogen bond to an oxygen of a neighboring riboside (O2-H2 O3 (1+ x, + y, + z): 2.694(2) Å). A hydroxyl oxygen of the hydrogen malate O16 forms a hydrogen bond with a hydroxyl and carbonyl oxygen of neighboring ribosides and O12 forms a hydrogen bond with a neighboring hydrogen malate oxygen (O16-H16 O12 (1 + x, + y, + z): 2.5449(11) Å). This hydrogen bond from O16 propagates through a chain of seven atoms ending with the acceptor atom O12.

#### Discussion of the hydrogen bonding network of **14**

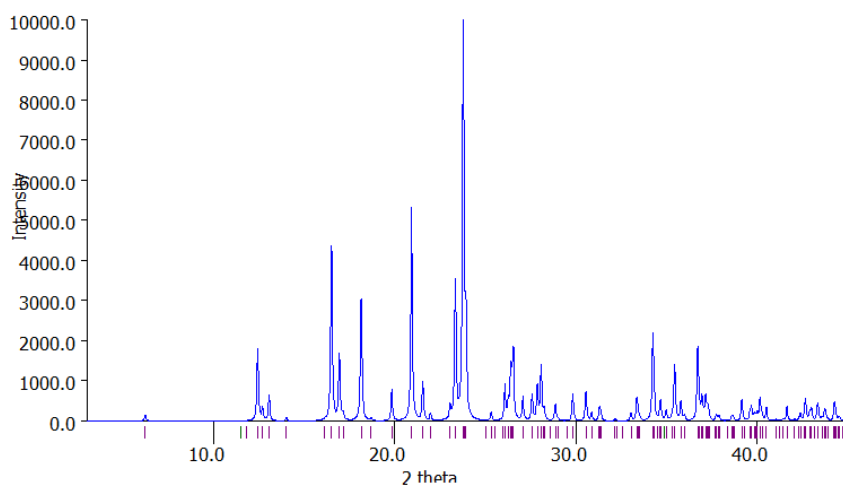
There are several hydrogen bonding motifs. The nitrogen of the amide group forms a hydrogen bond with hydroxyl oxygens of two neighboring hydrogen malate molecules (N2-H2A O15 (0.5 - x, -y, -0.5 + z): 3.005(2) Å, N2-H2B O14 (0.5 -x, 1 - y, - 0.5 + z): 3.024(2) Å). Hydroxyl oxygen atoms of the riboside O3 and O5 form hydrogen bonds with the hydrogen malate in the same asymmetric unit and to a neighboring hydrogen malate, respectively (O3-H3 O13: 2.677(2) Å, O5-H5 O13 (1 - x, 0.5 +y, 1.5 - z): 2.722(2) Å). Another hydroxyl oxygen of the riboside forms a hydrogen bond to an oxygen of a neighboring riboside (O2-H2 O3 (1 - x, -0.5 +y, 1.5 -z): 2.694(2) Å). The hydrogen bond from O2 propagates through a five-atom chain, ending again with the acceptor atom O3. Hydroxyl oxygen atoms of the hydrogen malate, O14 and O16 form hydrogen bonds, the first with a hydroxyl and carbonyl oxygen of neighboring ribosides, and the second with a neighboring hydrogen malate oxygen (O14-H14 O5 (-x, -0.5 + y, 1.5 - z): 2.887(2) Å, O14-H14 O1 (-x, 0.5 + y, 1.5 - z): 2.918(2) Å, O16-H16 O12 (+ x, -1 + y,+ z): 2.580(2) Å. The hydrogen bond beginning from O16-H16 propagates through 7 atoms before repeating with O16-H16 of the neighboring hydrogen malate (+x, -1 + y, + z).

(A)



(B)





(C)

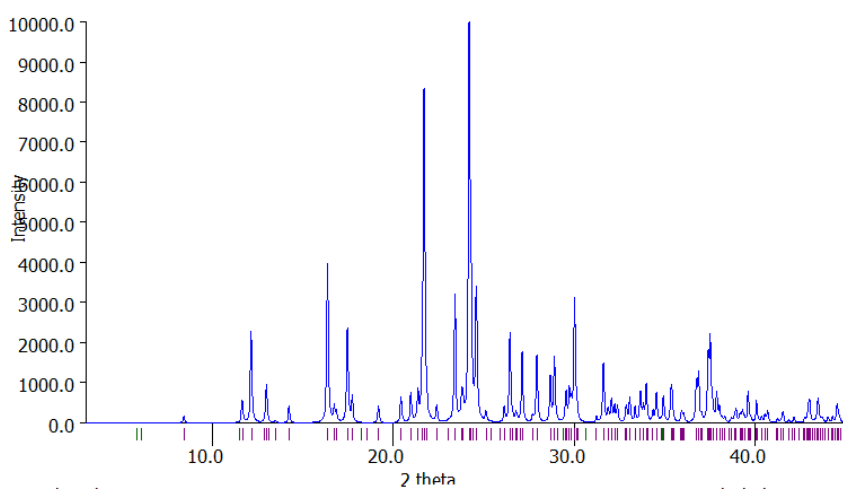
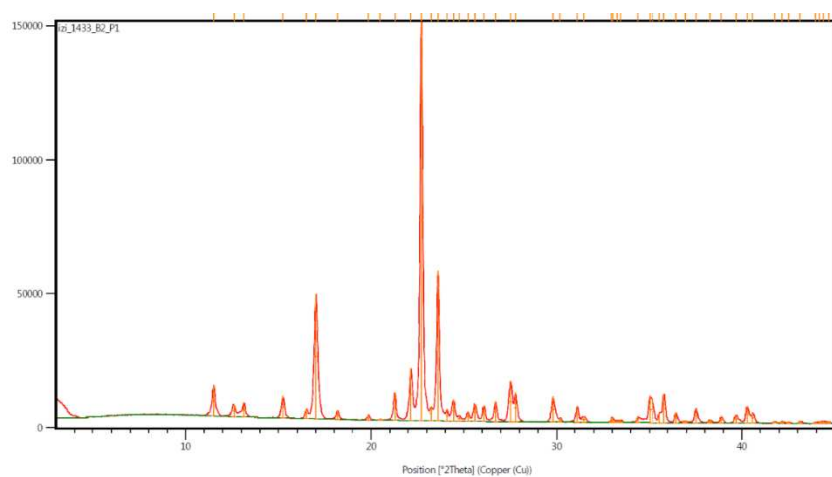


Figure S2: X-ray powder pattern of **11** (A). X-ray powder pattern of **11a** (anhydrous) simulated from single crystal data (B). X-ray powder pattern of **11b** (monohydrate) simulated from single crystal data (C).

(A)



(B)

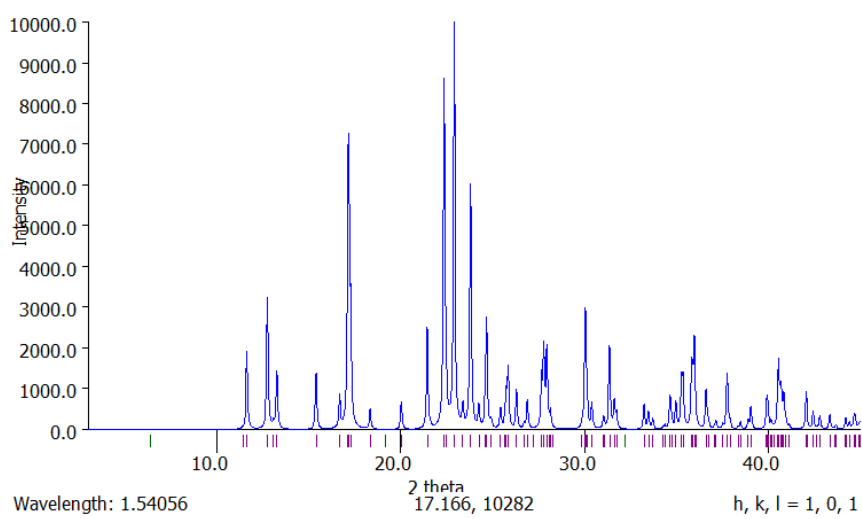
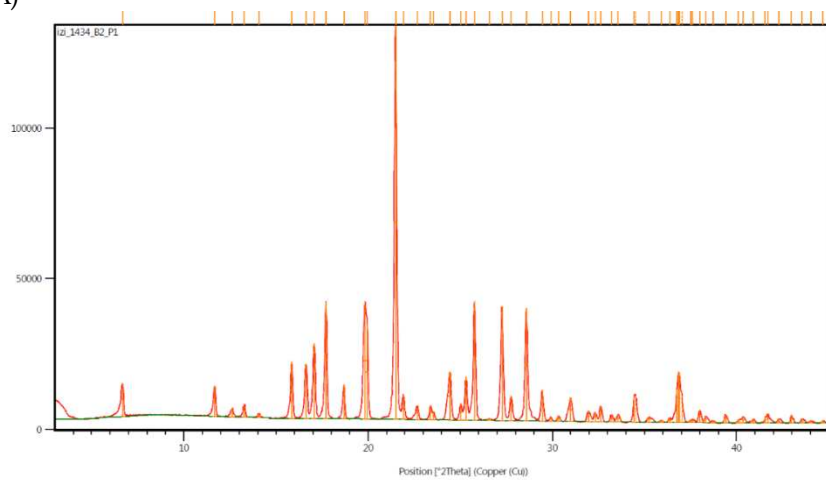


Figure S3: X-ray powder pattern of **12** (A). X-ray powder pattern of **12** simulated from single crystal data (B).

(A)



(B)

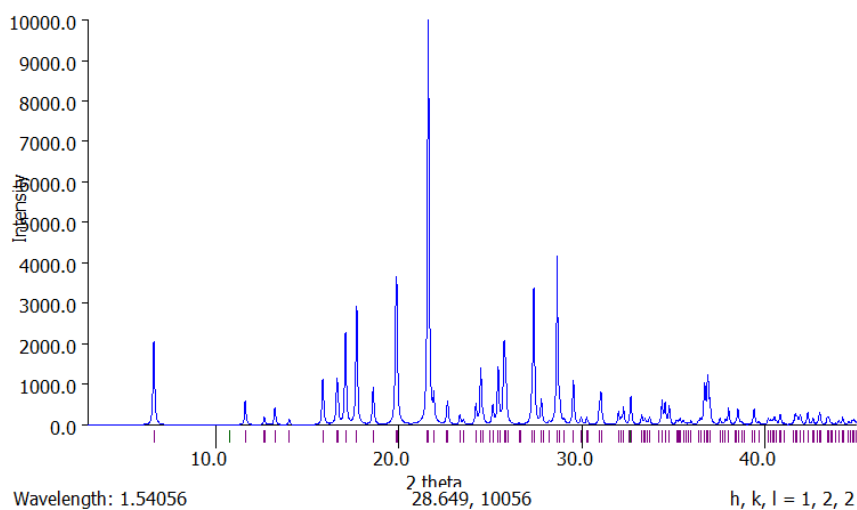
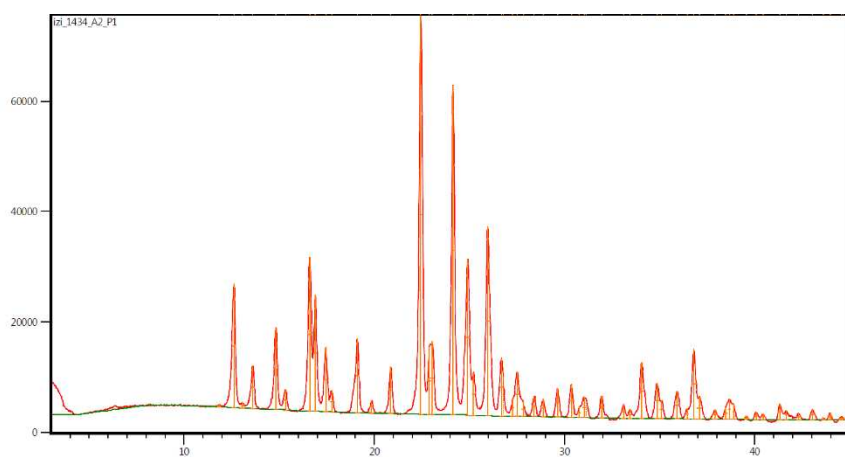


Figure S4: X-ray powder pattern of **13** (A). X-ray powder pattern of **13** simulated from single crystal data (B).

(A)



(B)

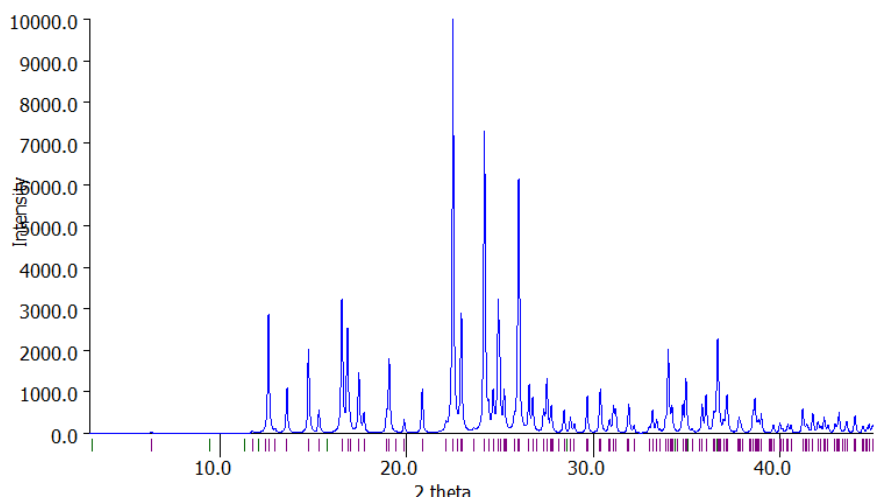
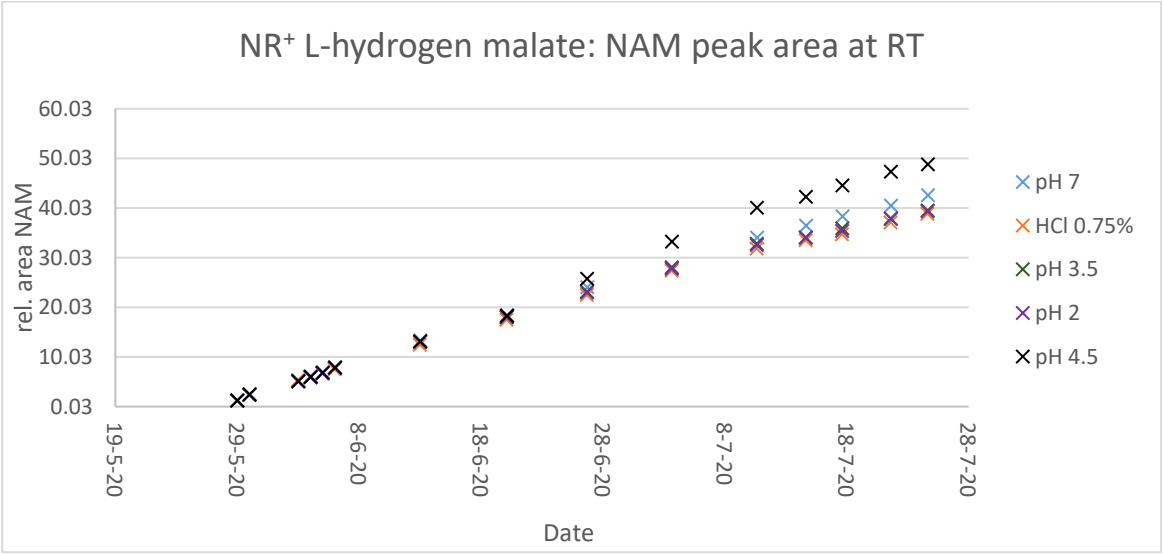


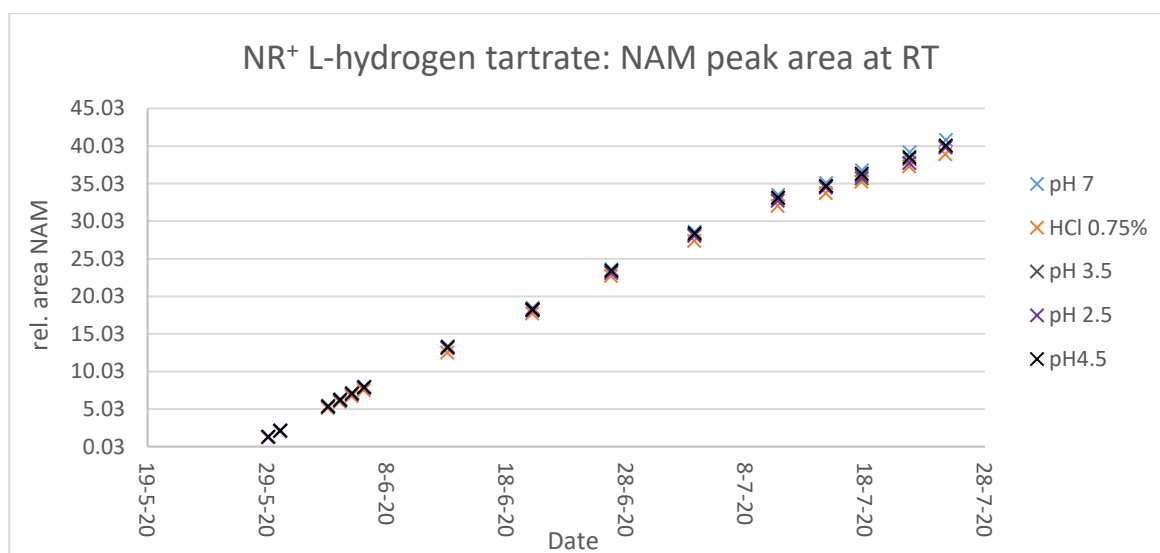
Figure S5: X-ray powder pattern of **14** (A). X-ray powder pattern of **14** simulated from single crystal data (B).

Section S5: Stability studies of NR<sup>+</sup> salts

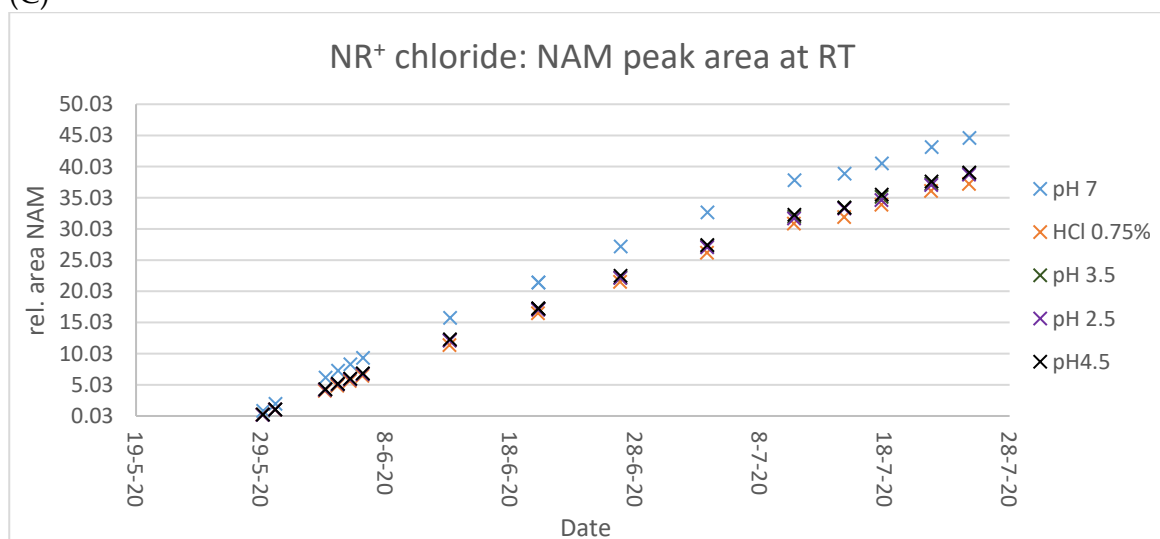
(A)



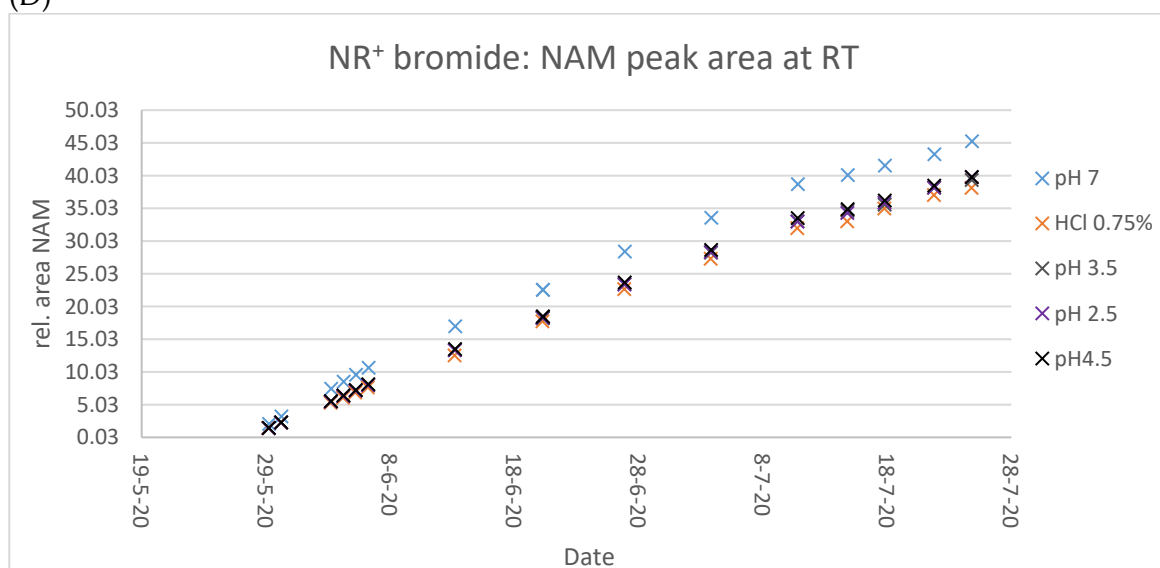
(B)



(C)



(D)



(E)

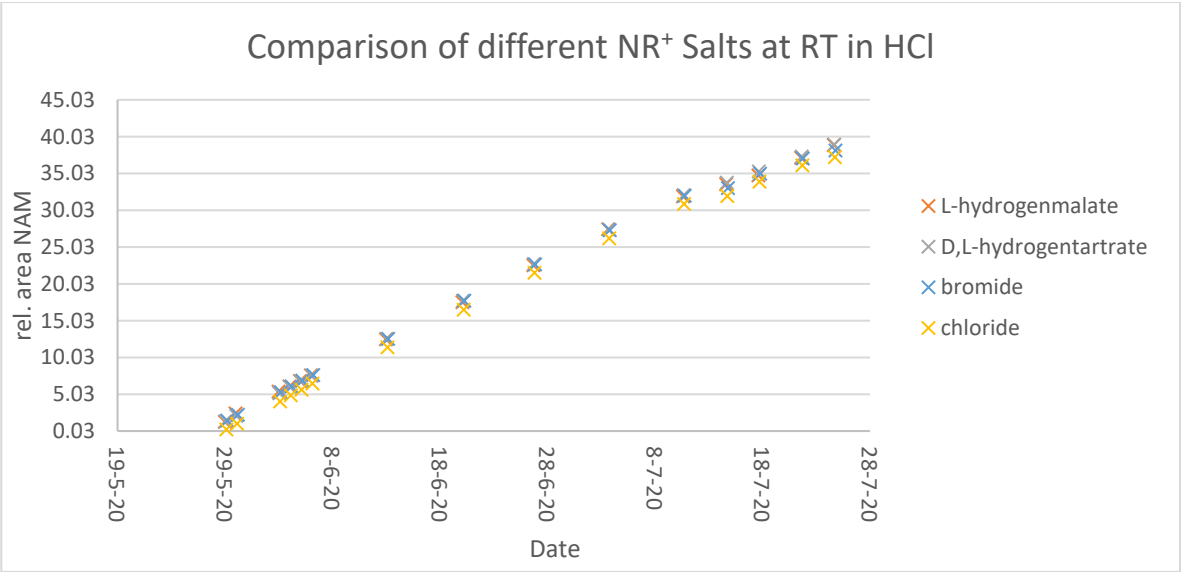
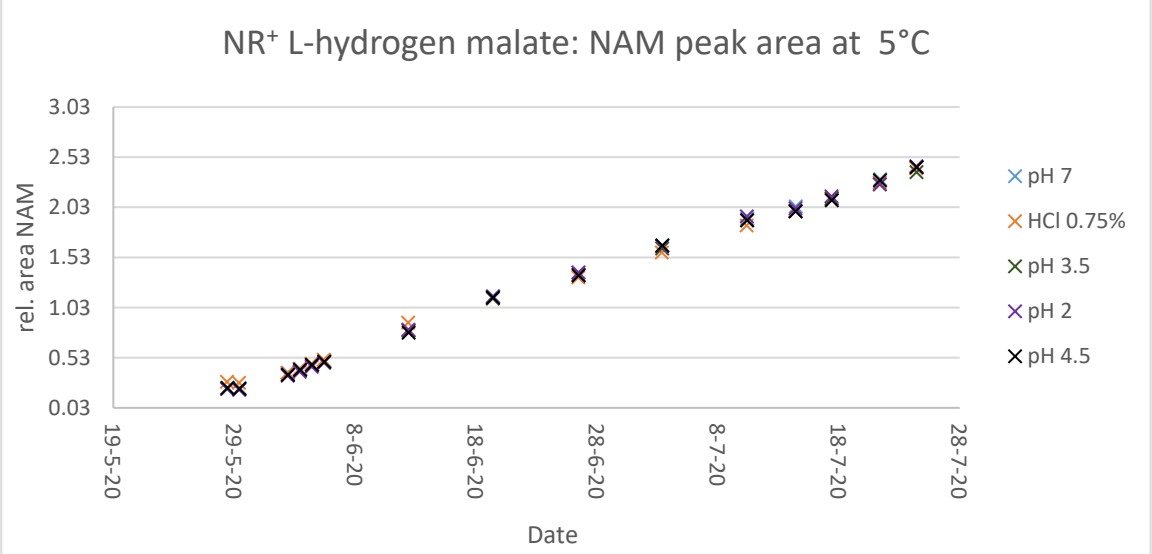
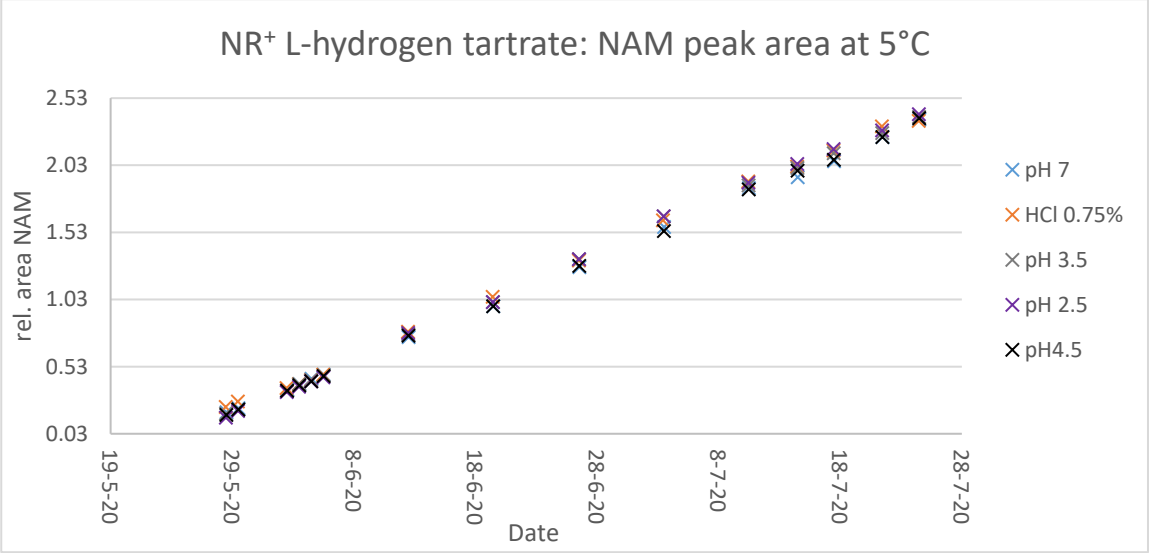


Figure S6: NAM peak area measurement over time at RT at various pH for NR<sup>+</sup> L-hydrogen malate (A), NR<sup>+</sup> D,L-hydrogen tartrate (B), NR<sup>+</sup> chloride (C), NR<sup>+</sup> bromide (D); Comparison of the different NR<sup>+</sup> Salts at RT in HCl (E).

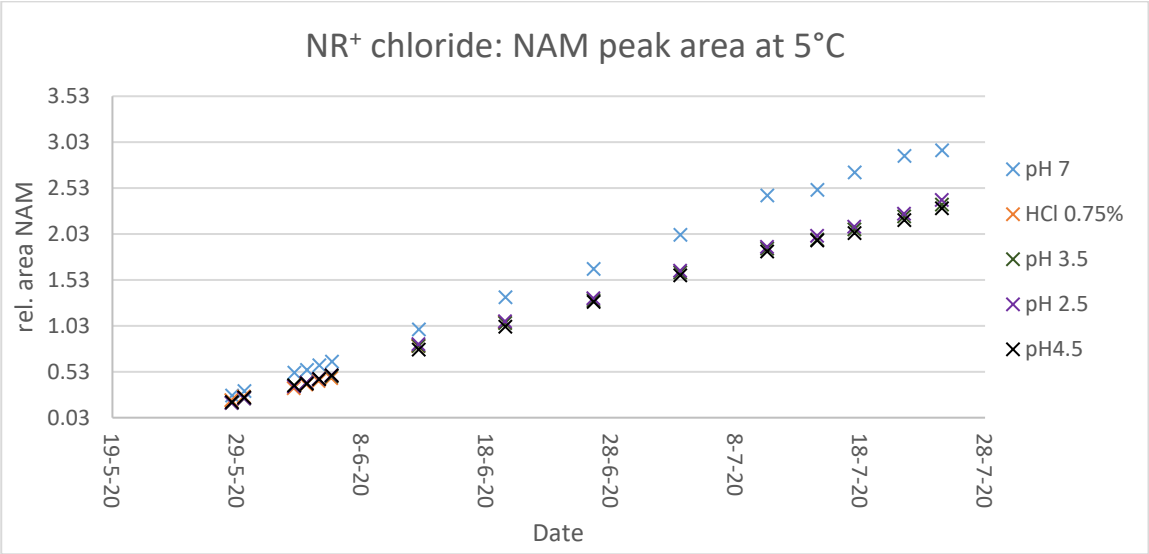
(A)



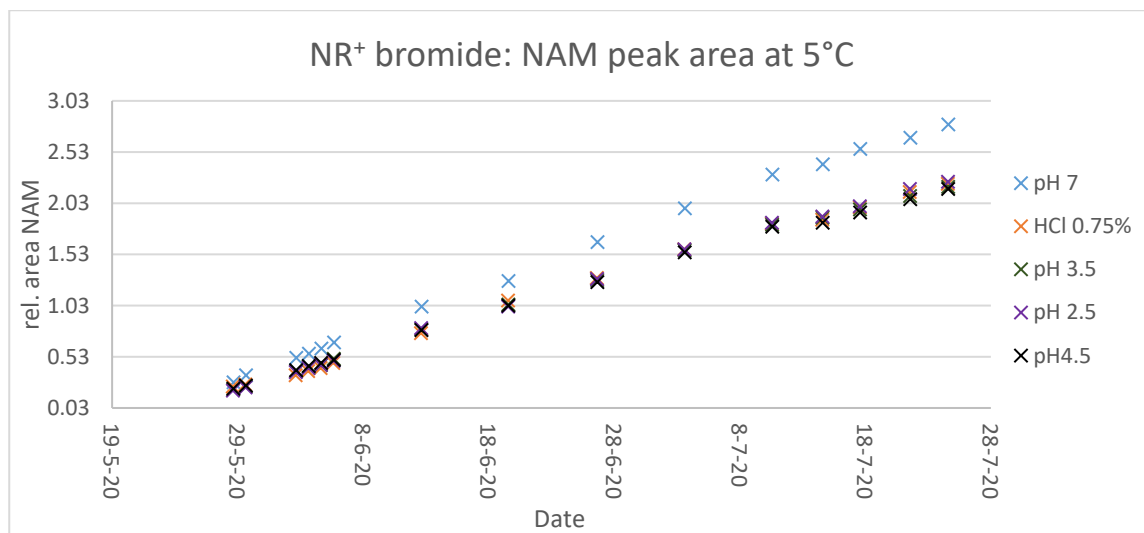
(B)



(C)



(D)



(E)

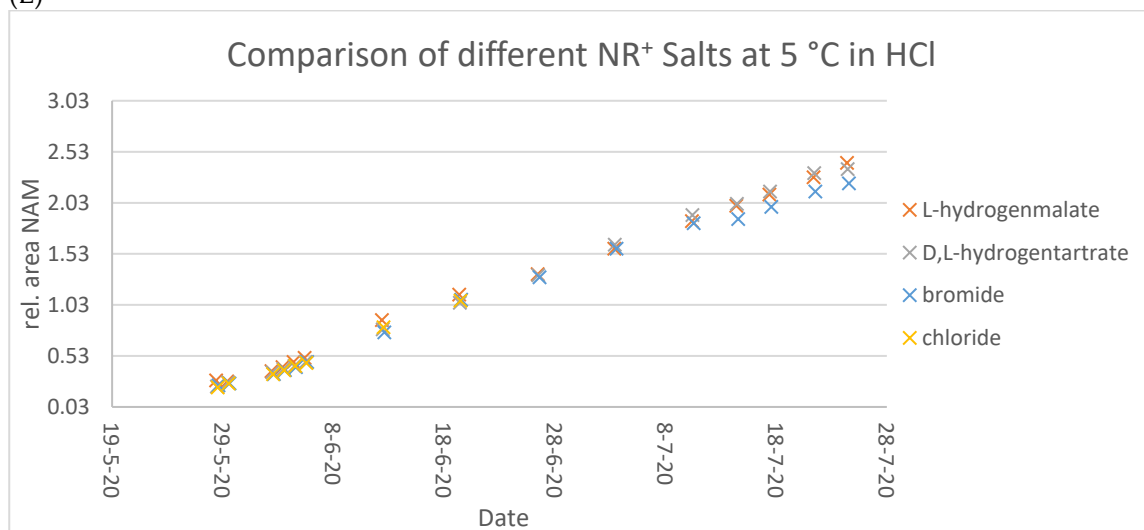
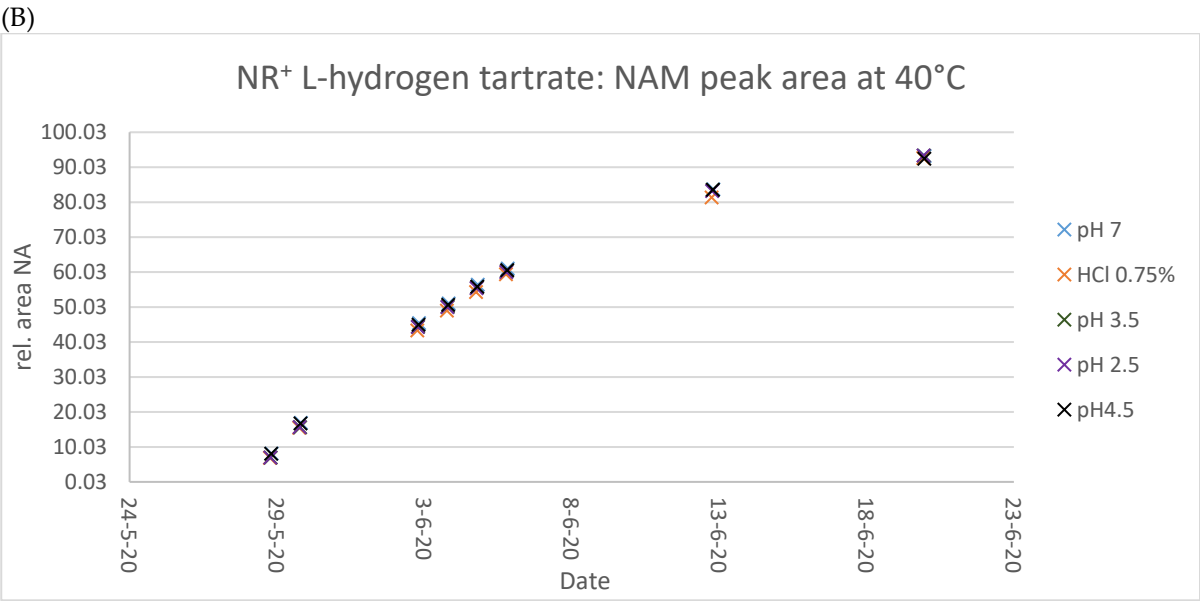
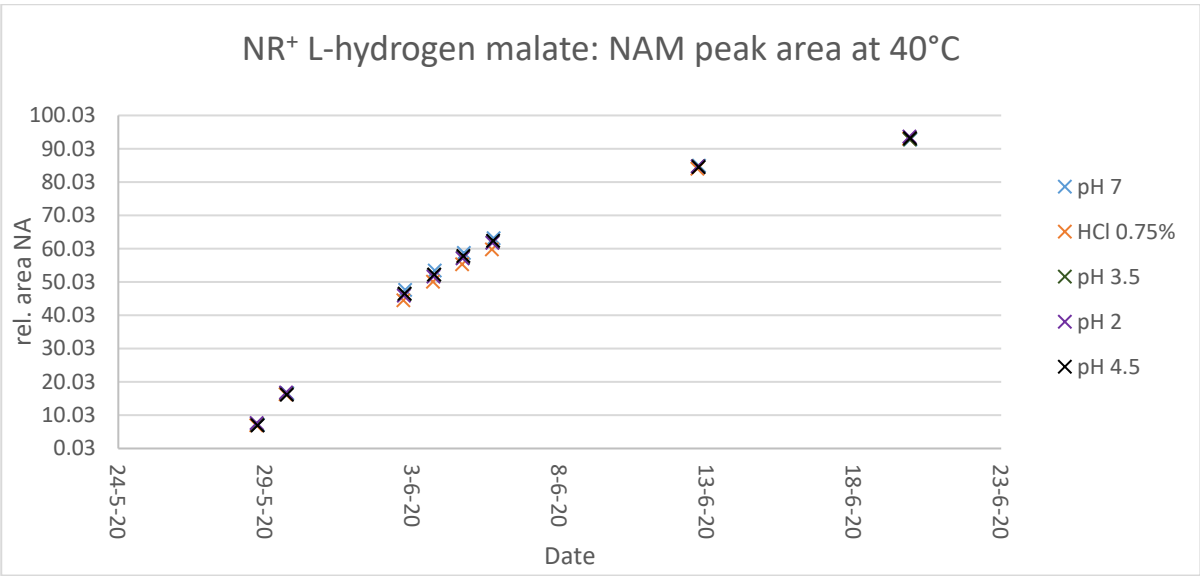


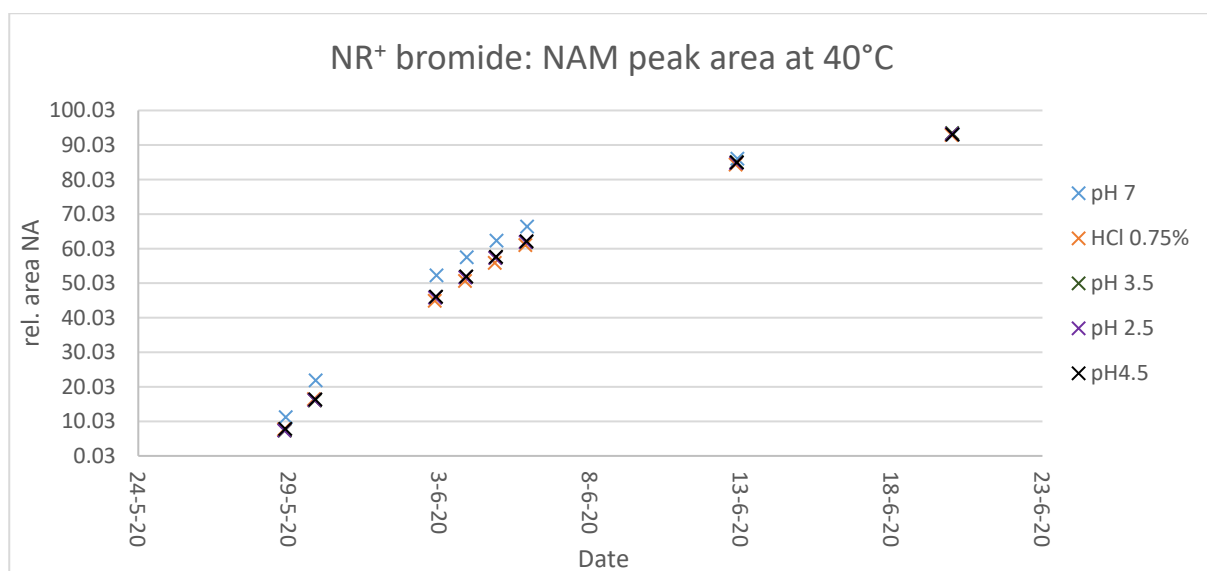
Figure S7: NAM peak area measurement over time at 5 °C at various pH for NR<sup>+</sup> L-hydrogen malate (A), NR<sup>+</sup> D,L-hydrogen tartrate (B), NR<sup>+</sup> chloride (D), NR<sup>+</sup> bromide (E); Comparison of the different NR<sup>+</sup> Salts at 5 °C in HCl (F).

(A)

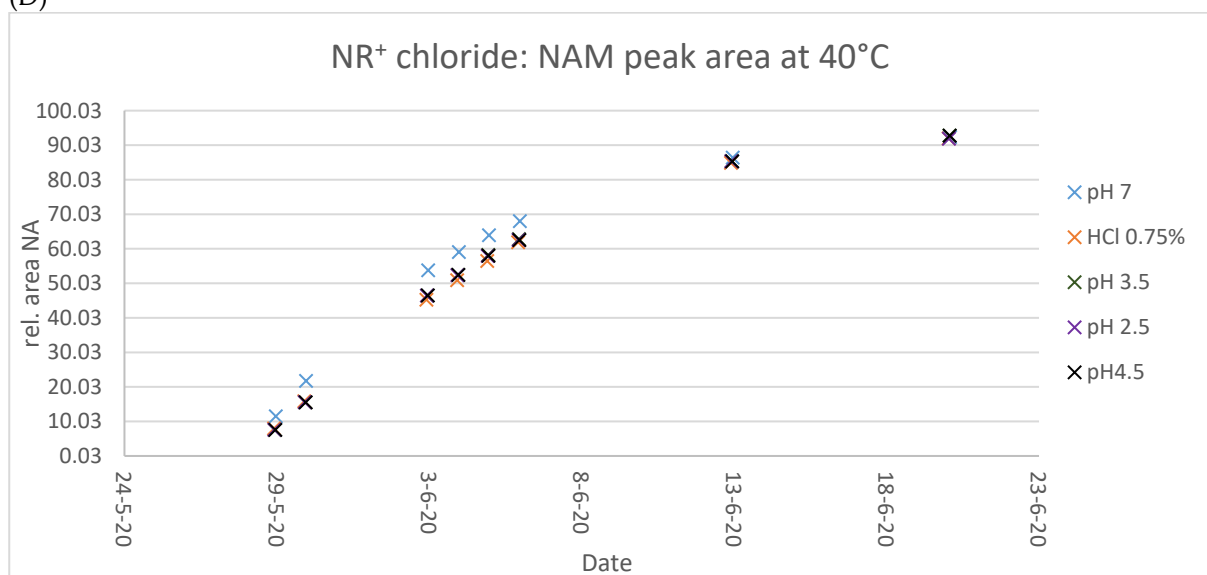




(C)



(D)



(E)

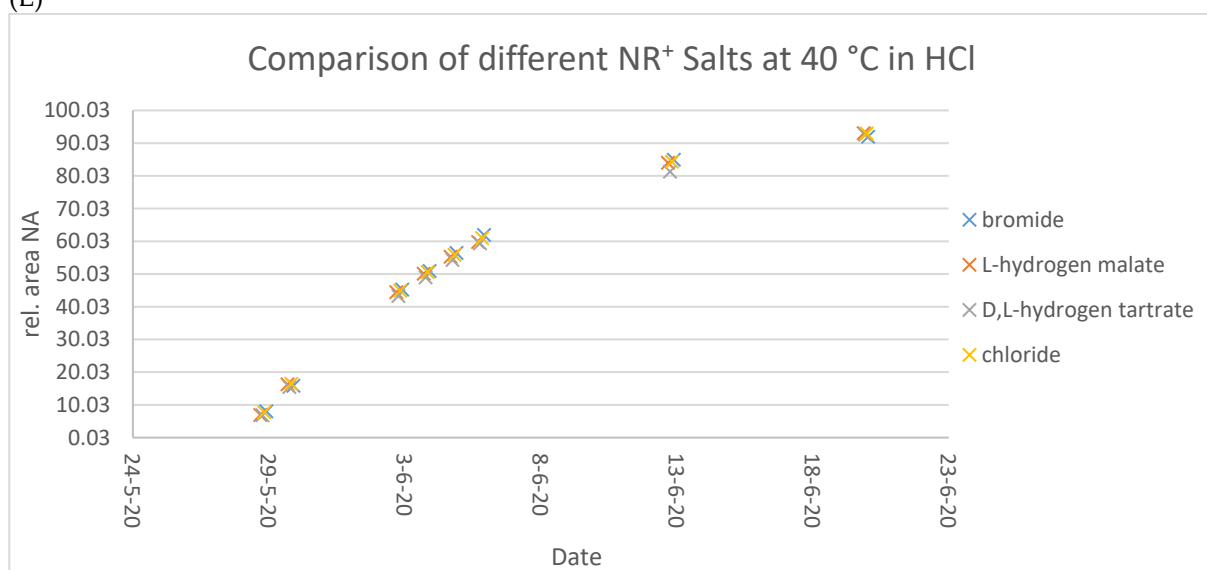
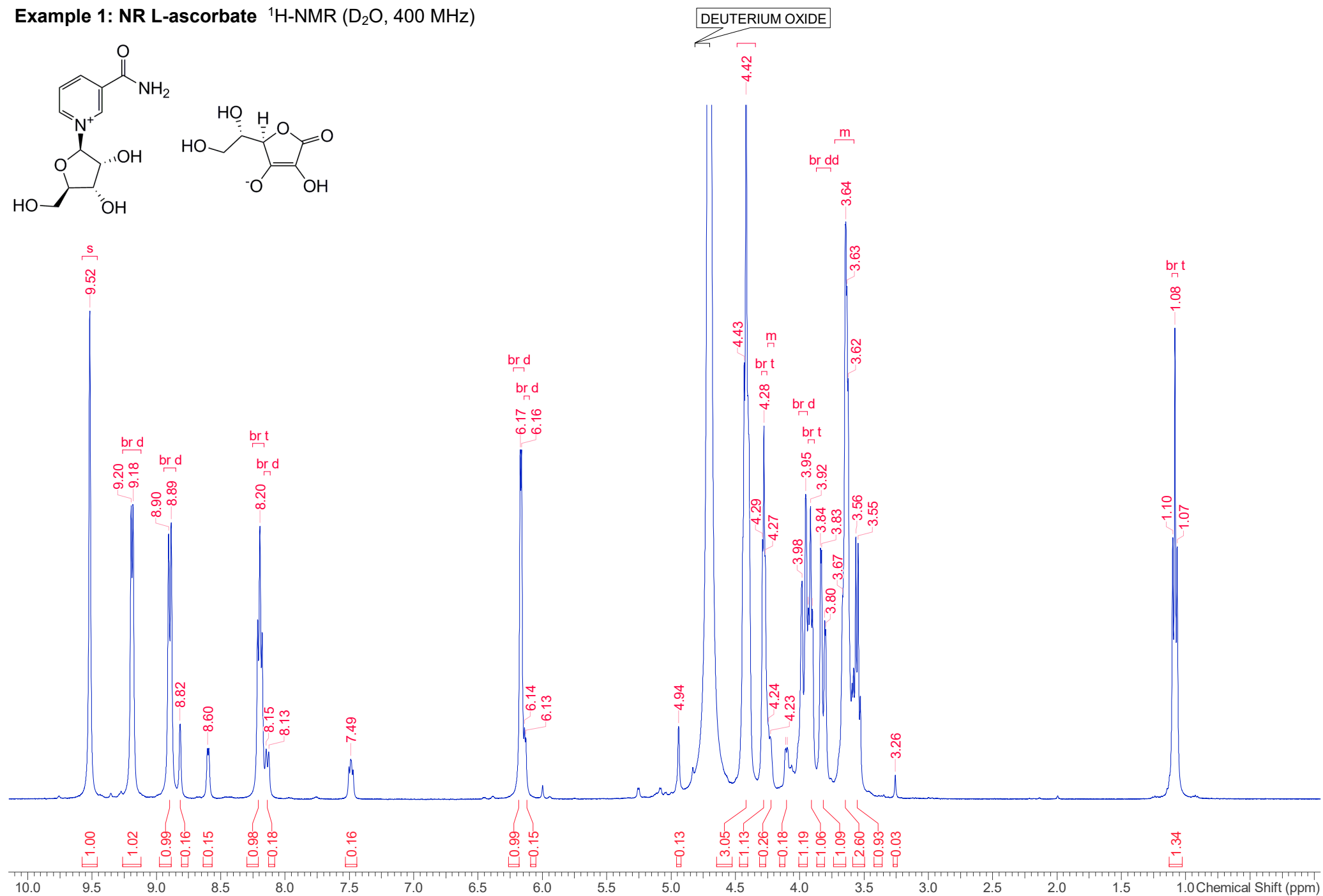
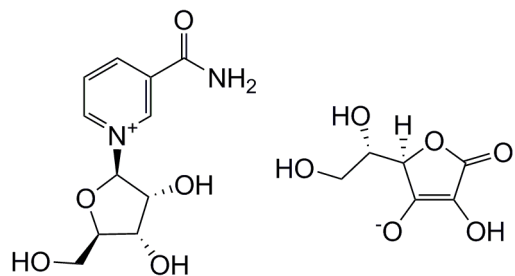
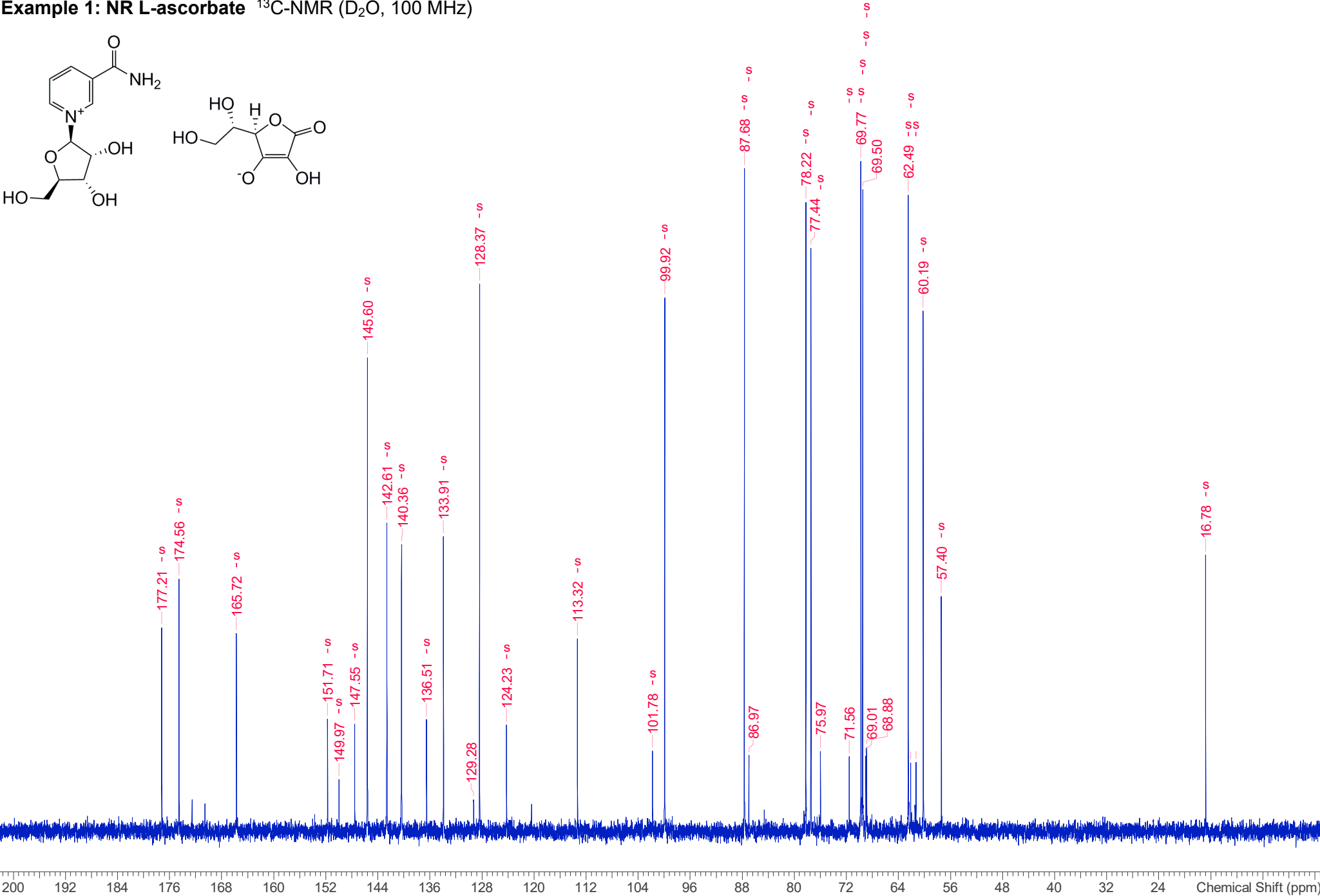
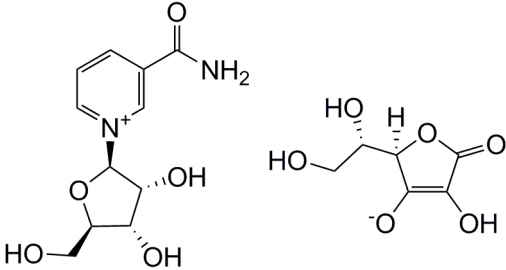


Figure S8: NAM peak area measurement over time at 40 °C at various pH for NR<sup>+</sup> L-hydrogen malate (A), NR<sup>+</sup> D,L-hydrogen tartrate (B), NR<sup>+</sup> chloride (D), NR<sup>+</sup> bromide (E); Comparison of the different NR<sup>+</sup> Salts at 40 °C in HCl (F).

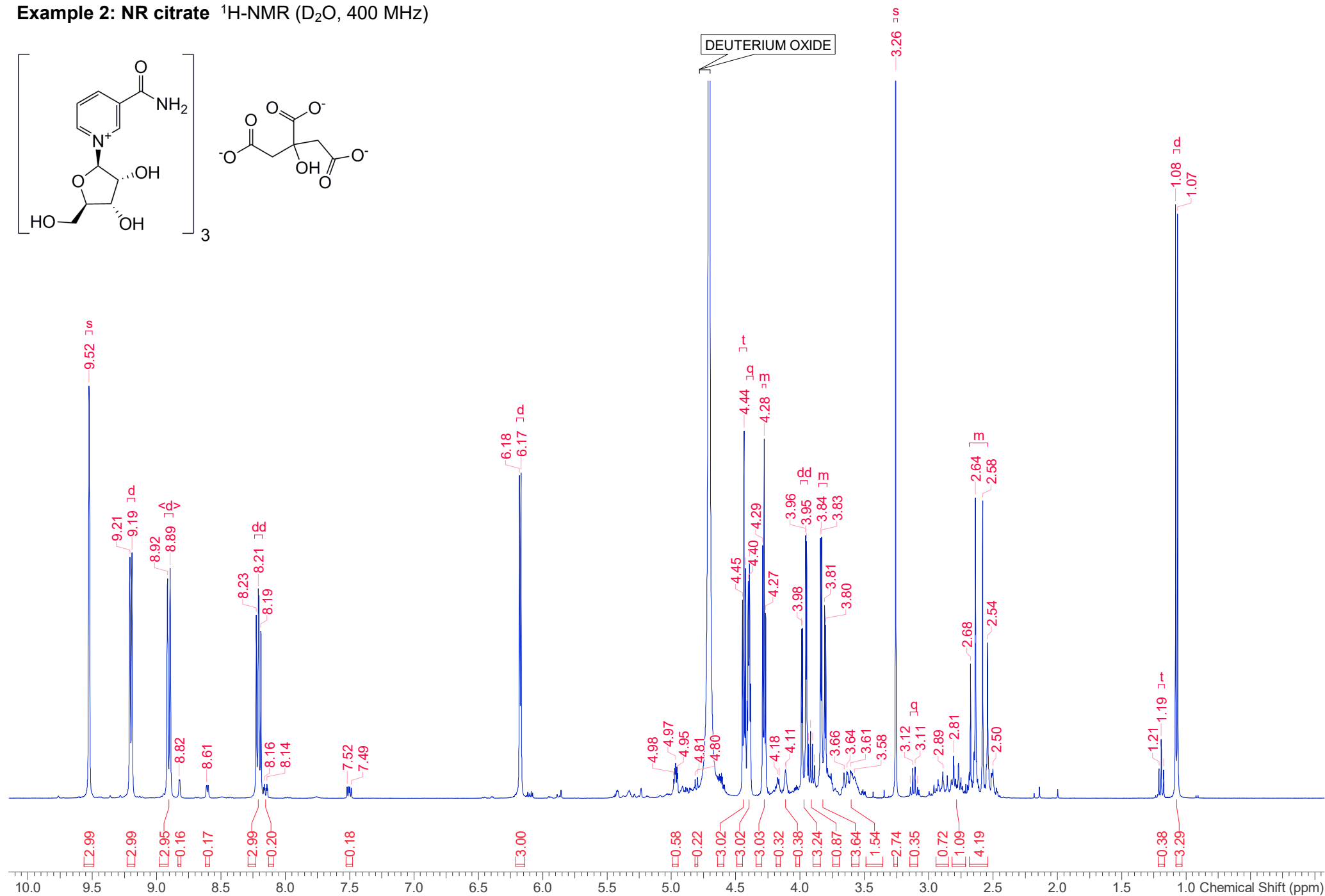
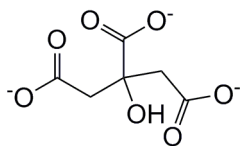
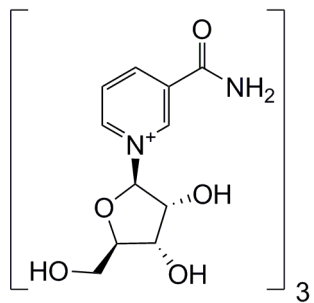
**Example 1: NR L-ascorbate**  $^1\text{H}$ -NMR ( $\text{D}_2\text{O}$ , 400 MHz)



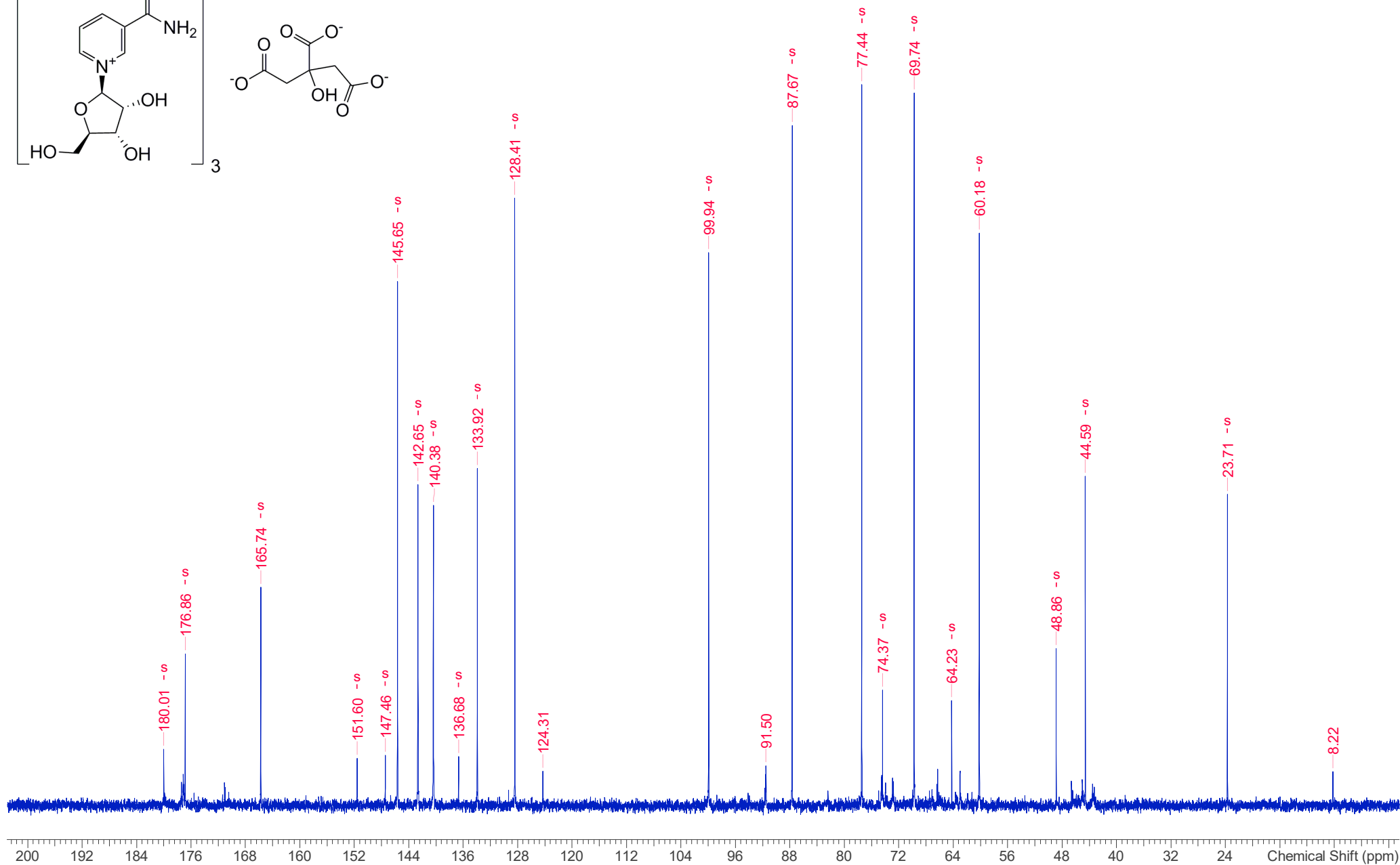
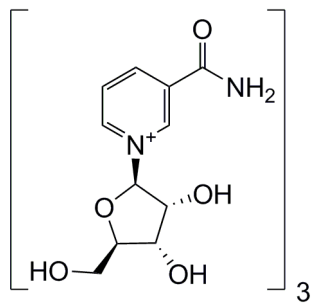
Example 1: NR L-ascorbate <sup>13</sup>C-NMR (D<sub>2</sub>O, 100 MHz)



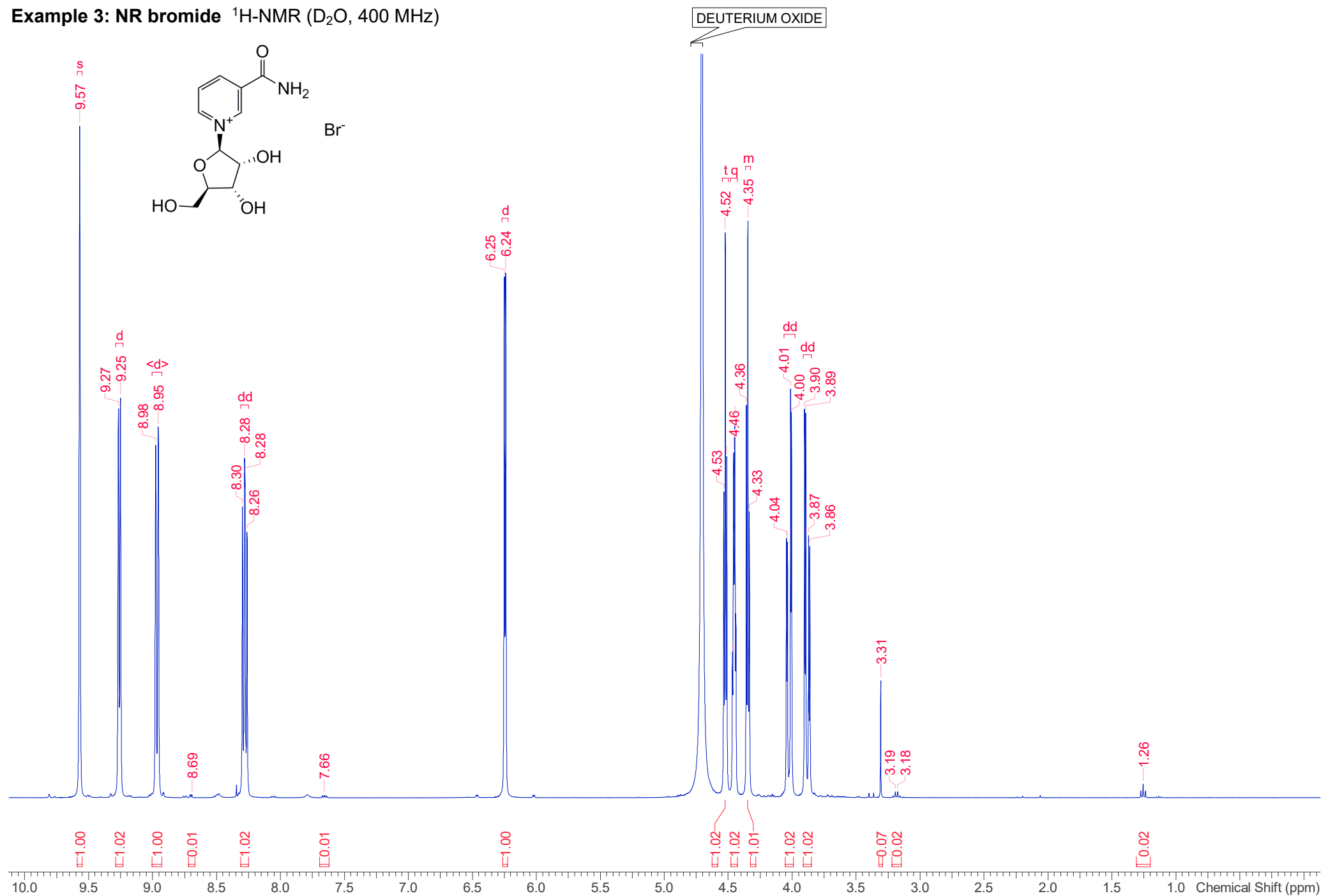
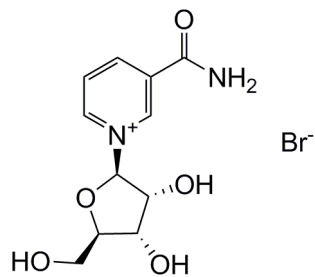
**Example 2: NR citrate**  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ , 400 MHz)



**Example 2: NR citrate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)

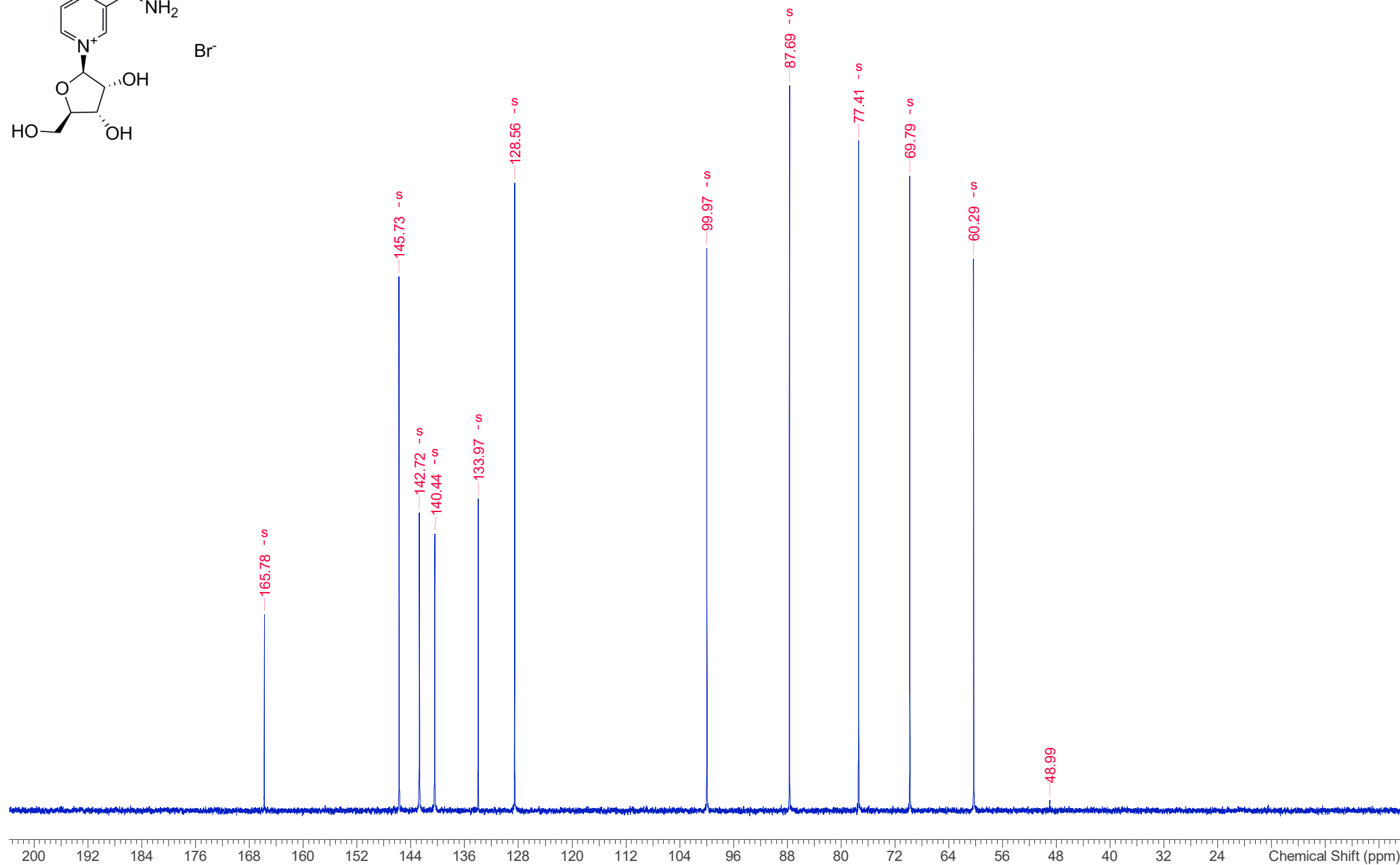
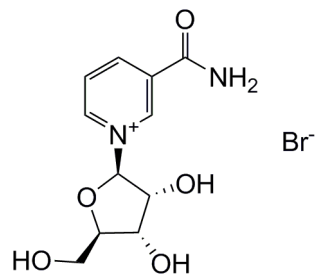


**Example 3: NR bromide**  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ , 400 MHz)

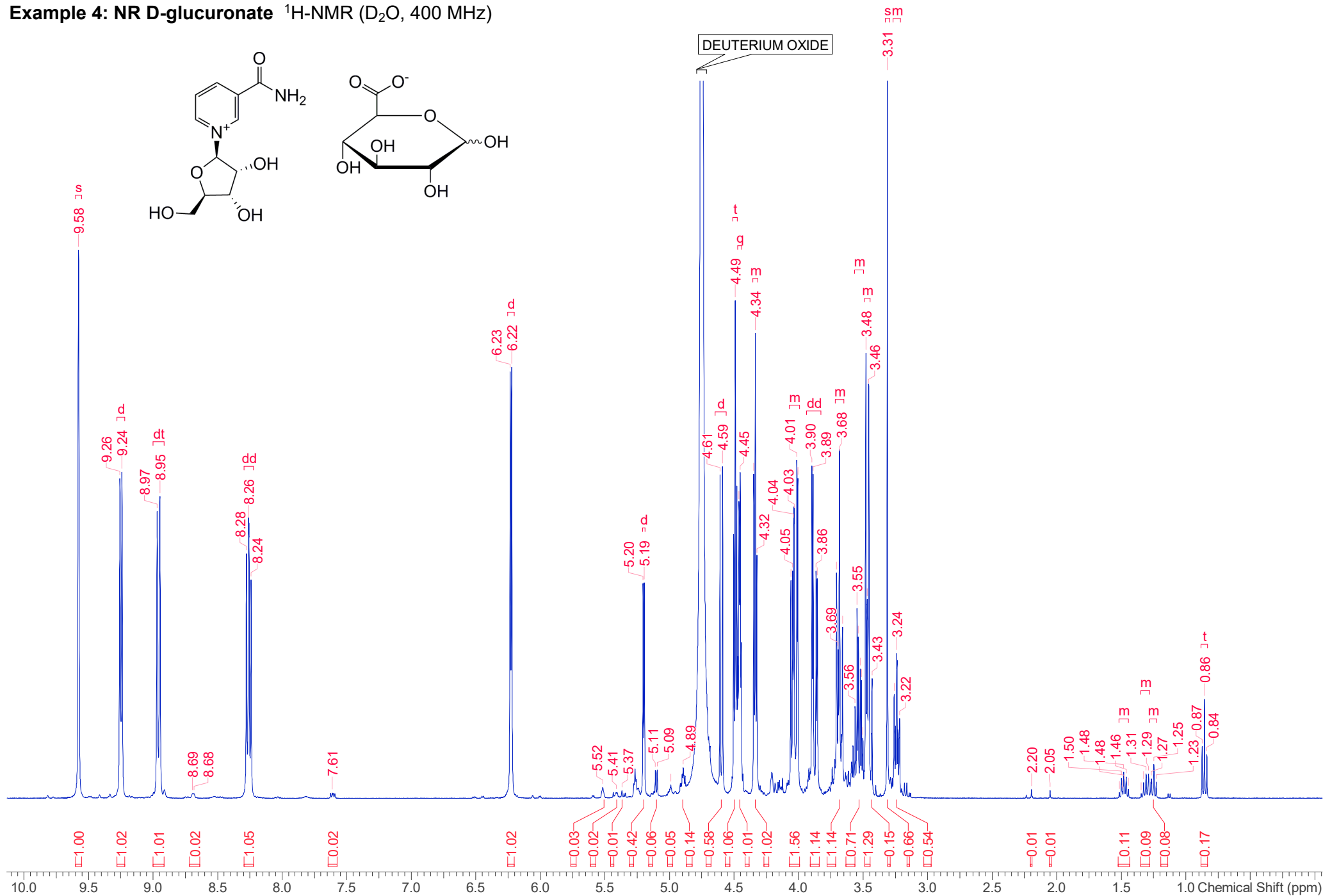
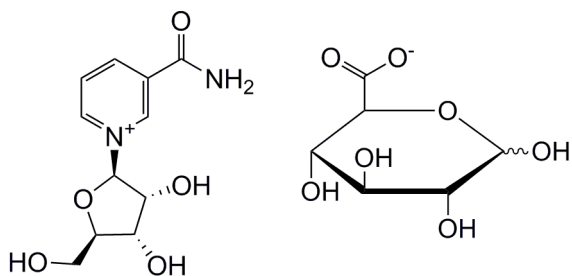




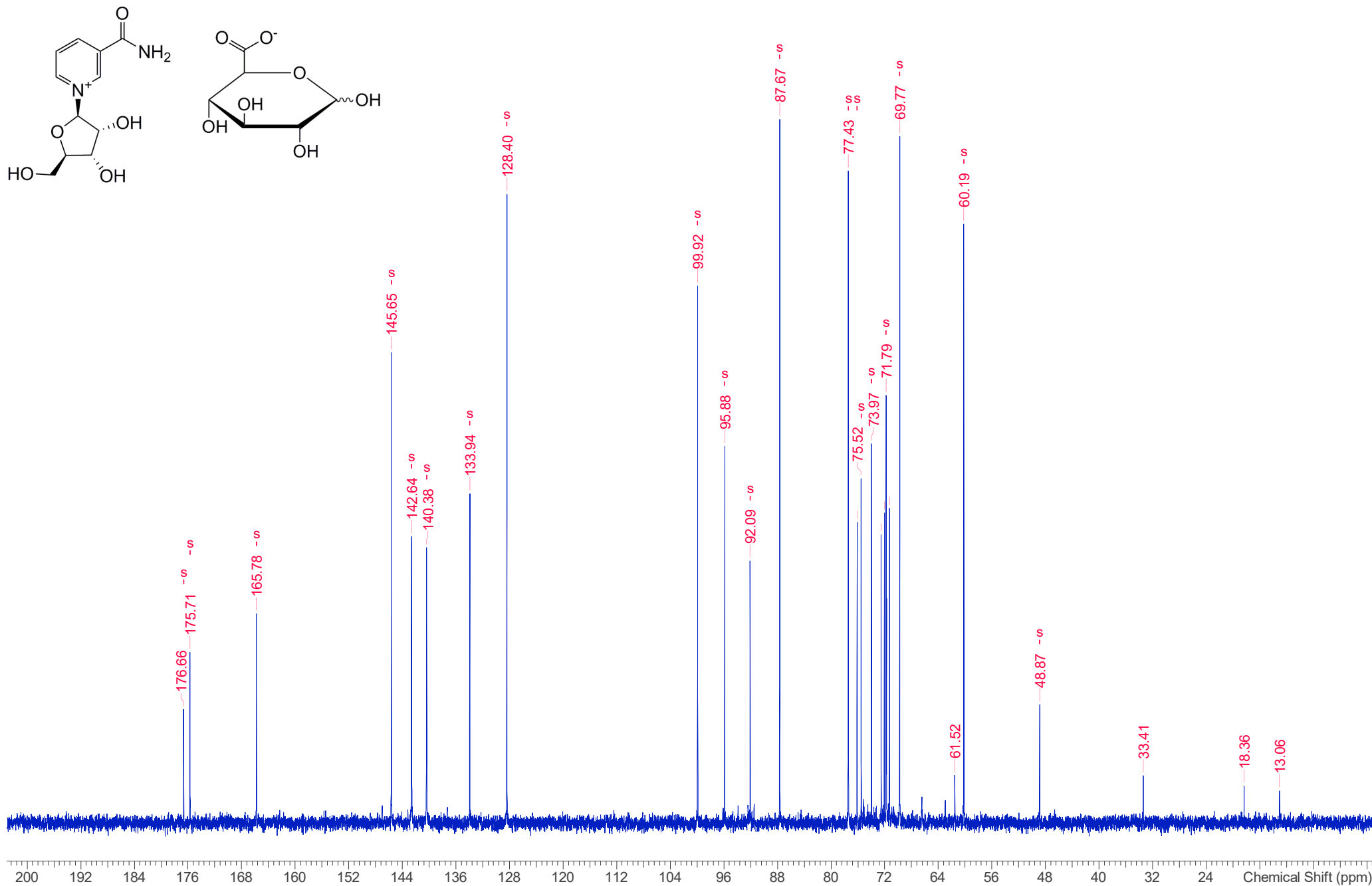
**Example 3: NR bromide**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)



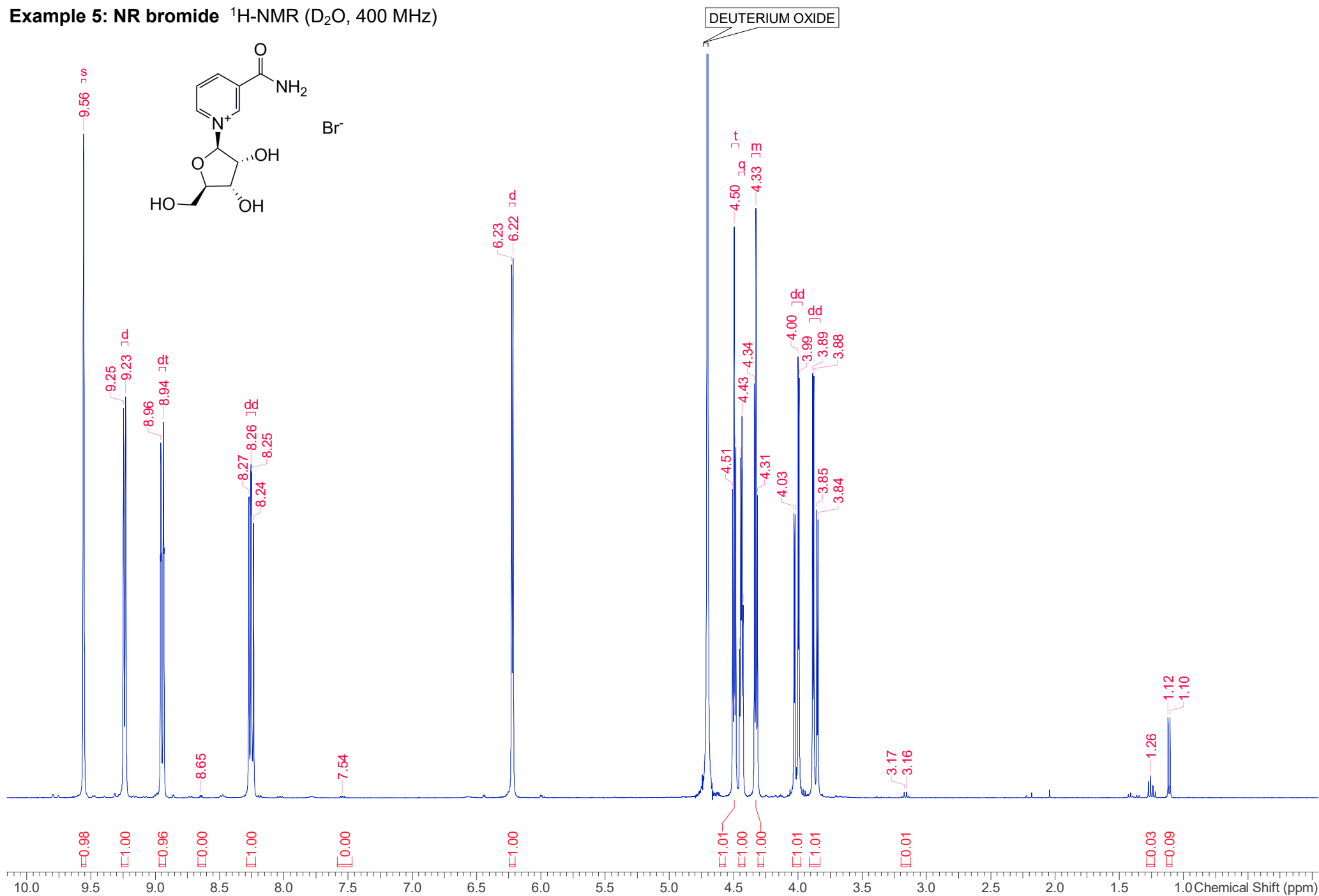
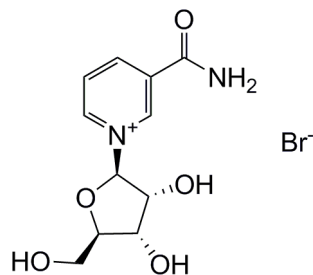
**Example 4: NR D-glucuronate**  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ , 400 MHz)



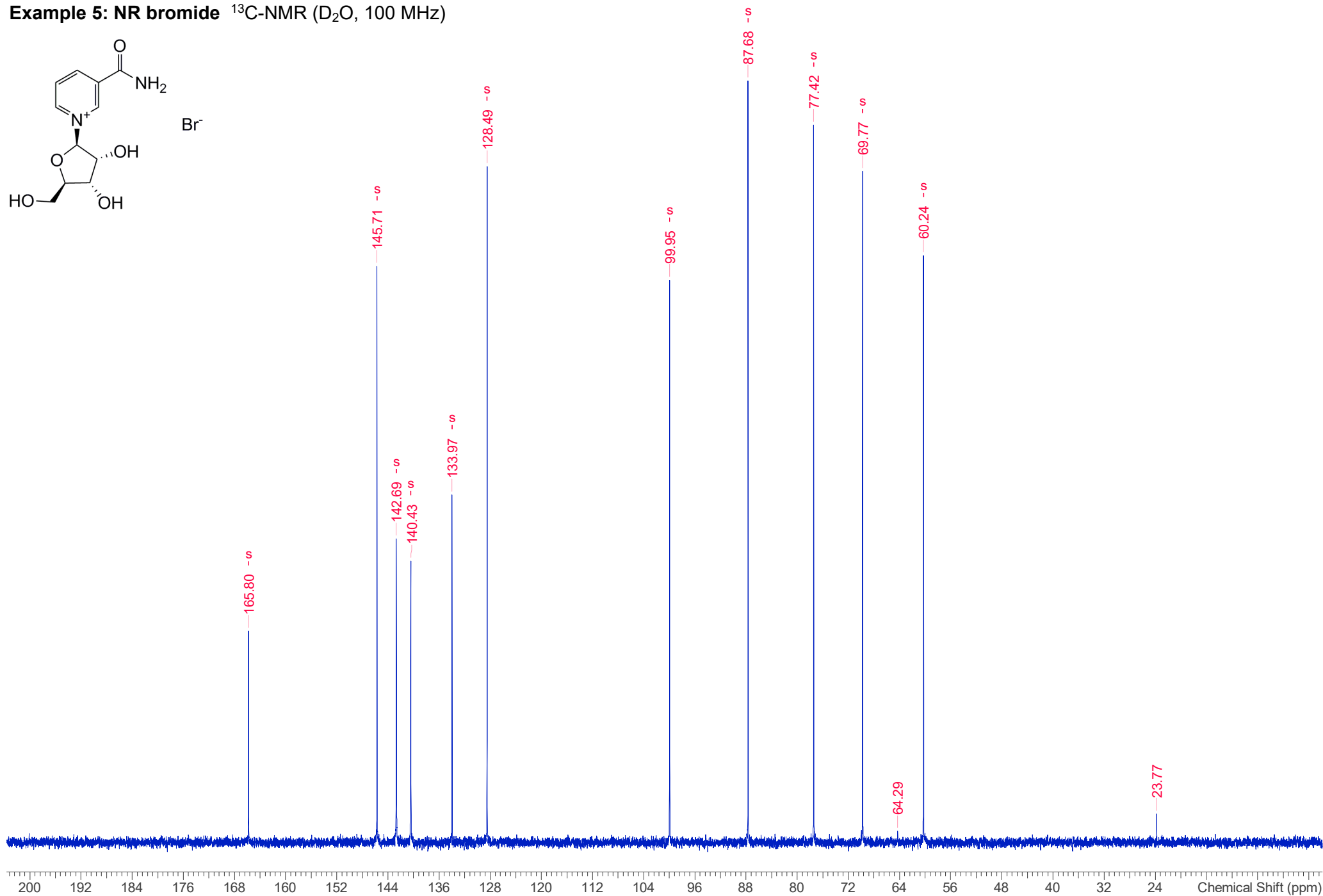
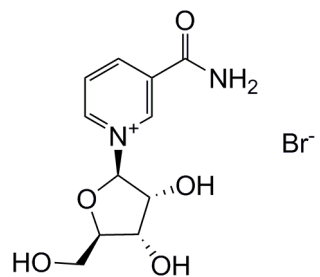
**Example 4: NR D-glucuronate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)



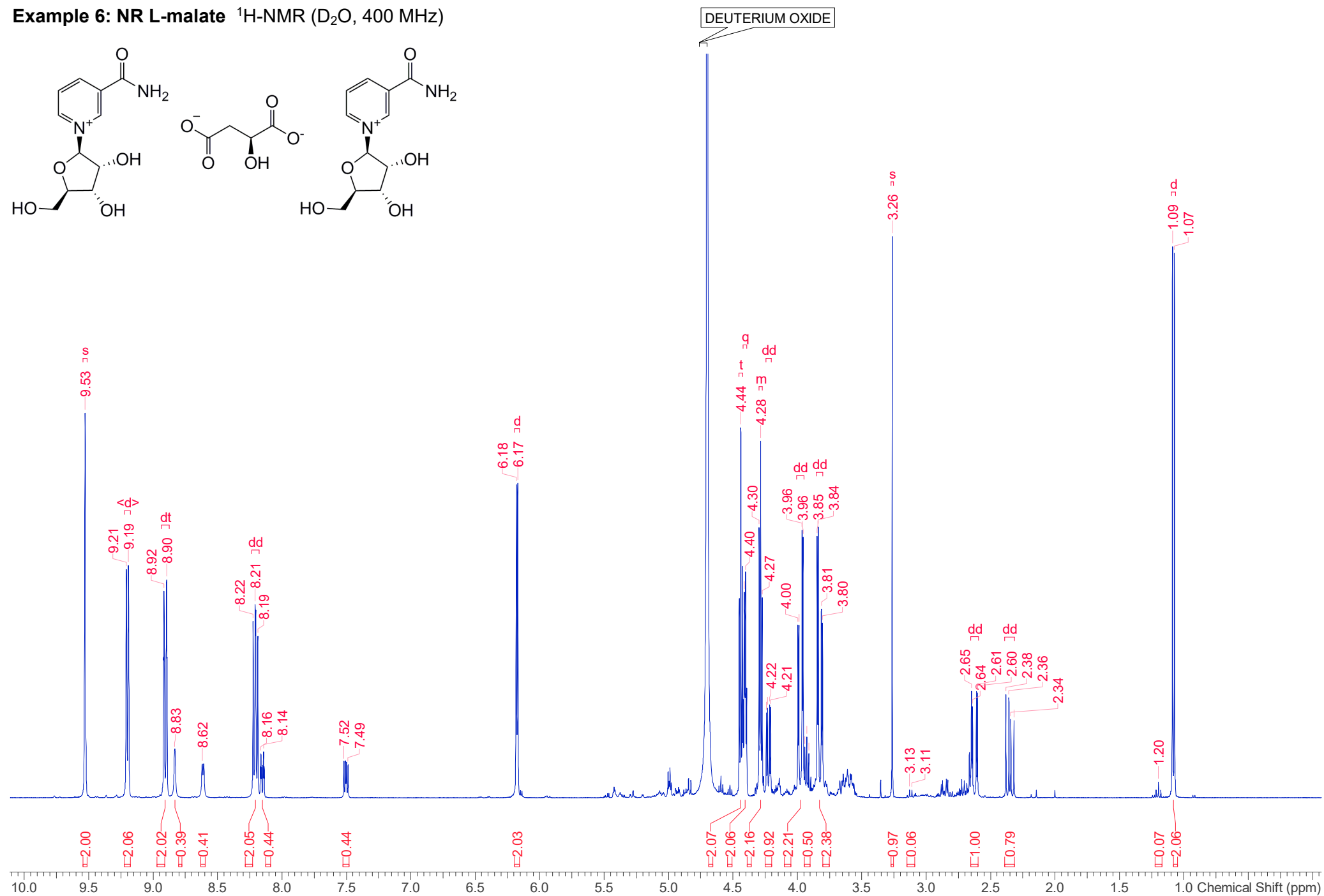
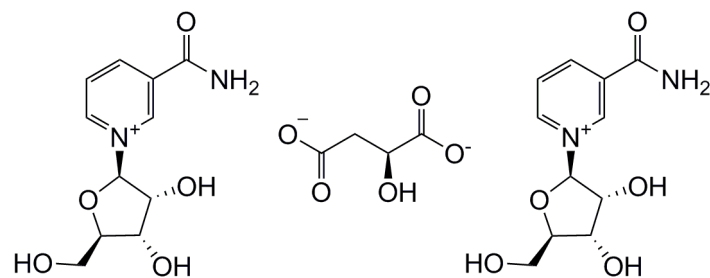
**Example 5: NR bromide**  $^1\text{H}$ -NMR ( $\text{D}_2\text{O}$ , 400 MHz)



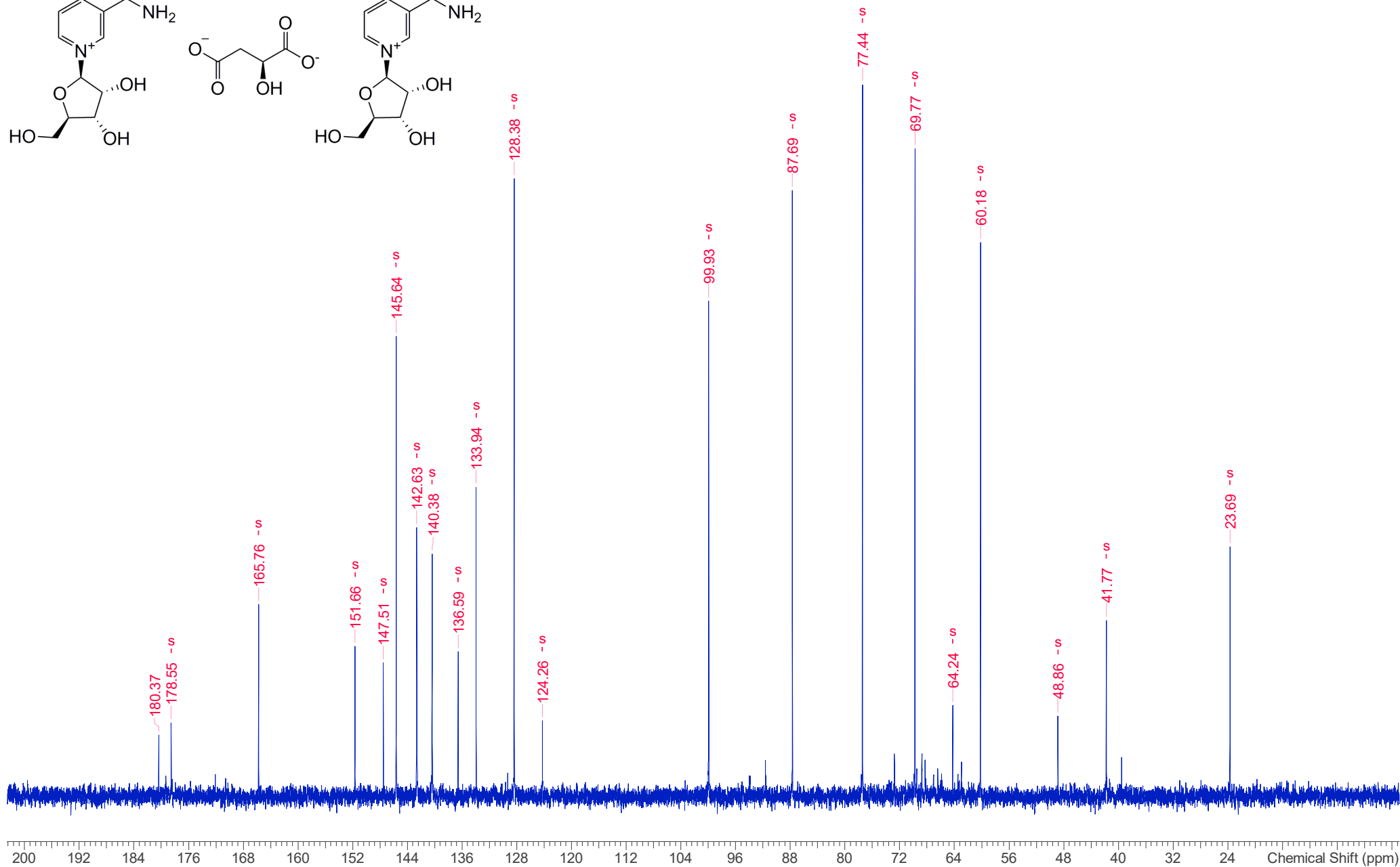
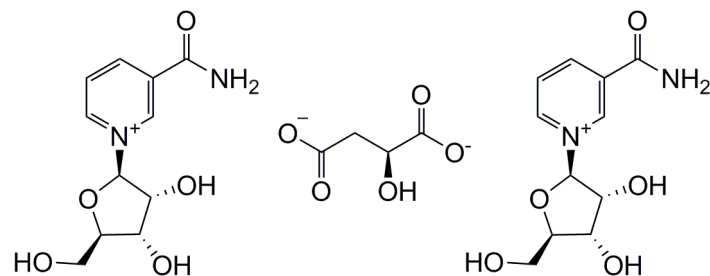
**Example 5: NR bromide**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)



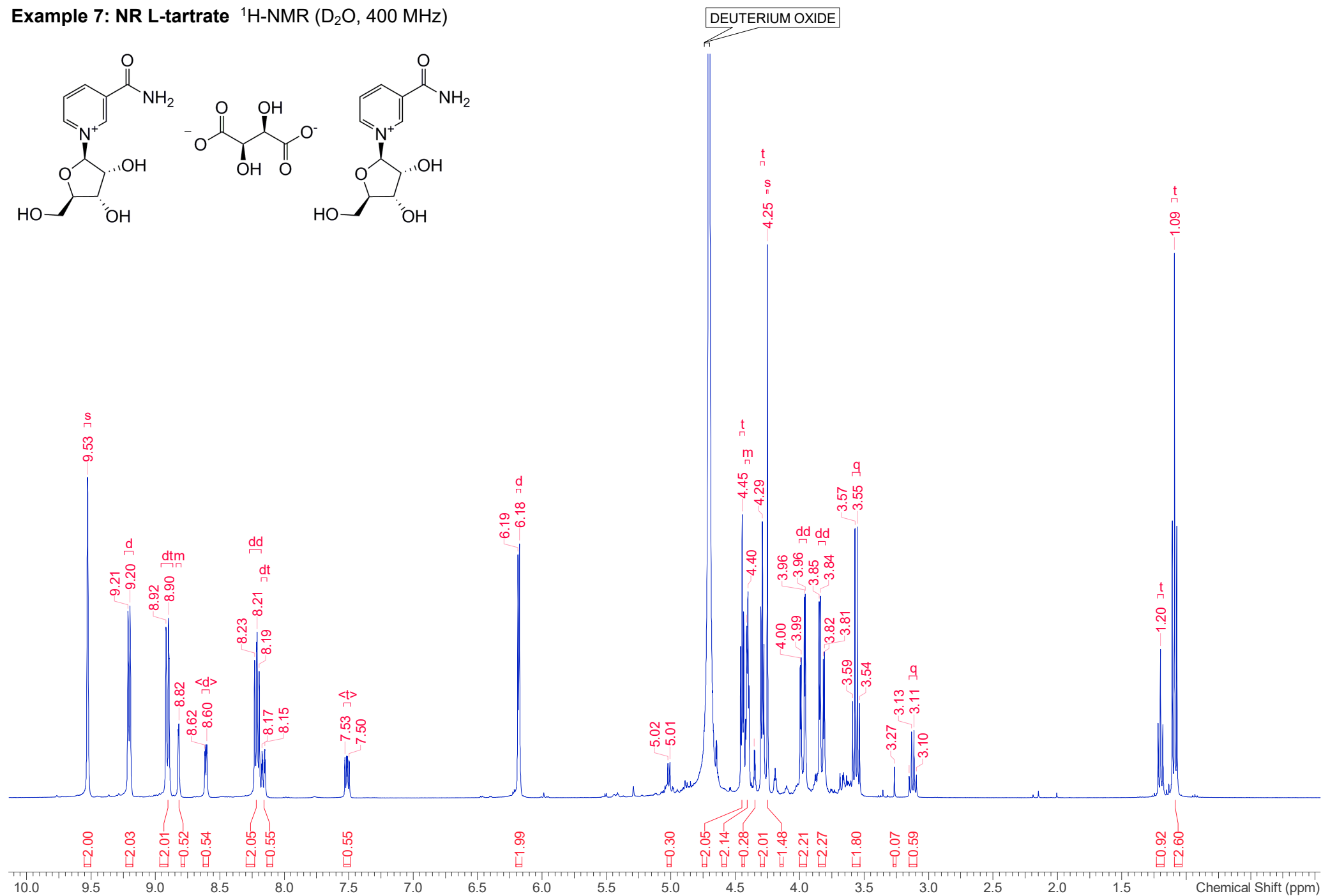
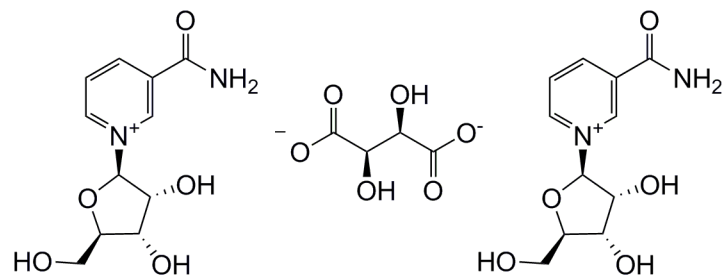
**Example 6: NR L-malate**  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ , 400 MHz)



**Example 6: NR L-malate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)

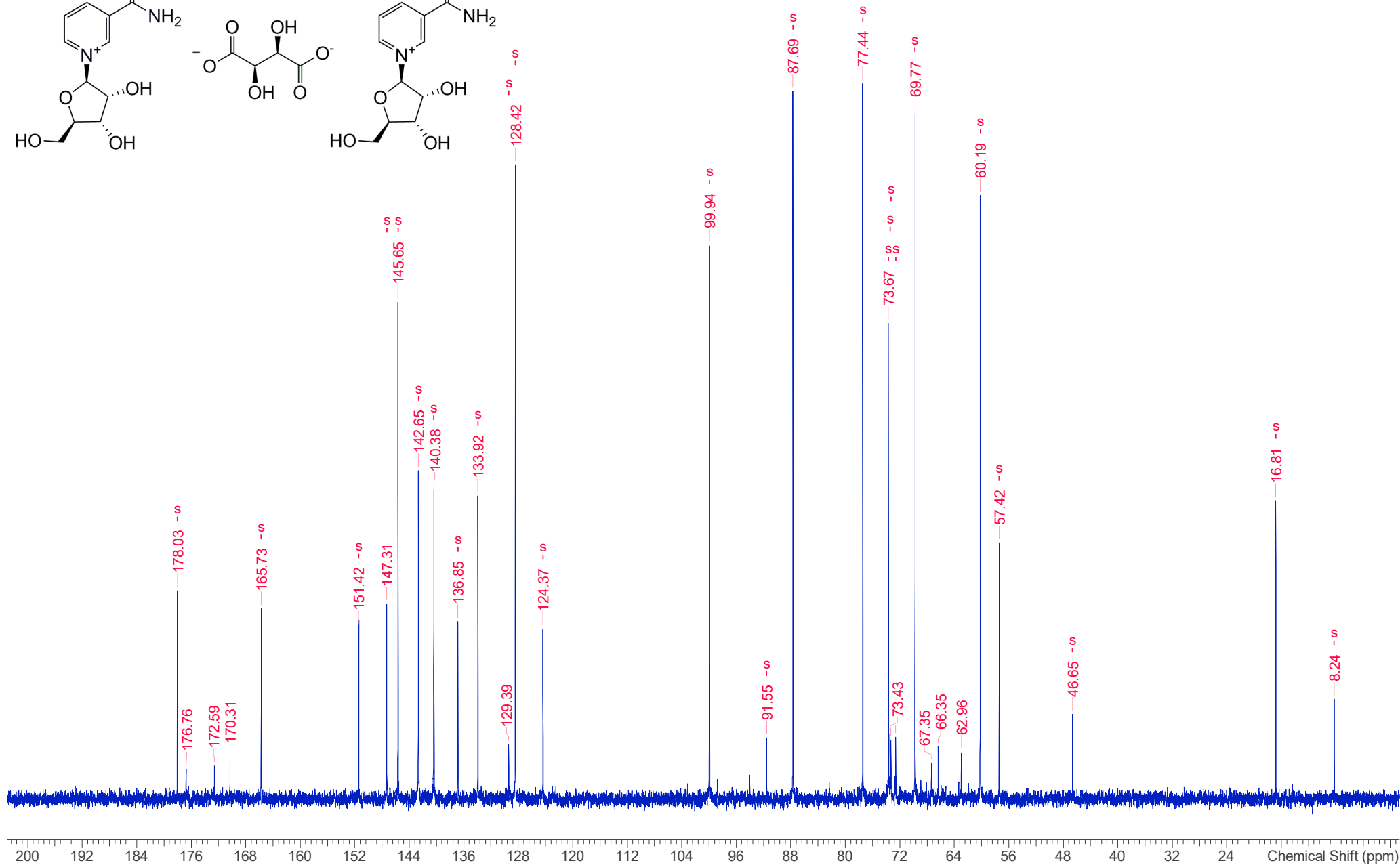
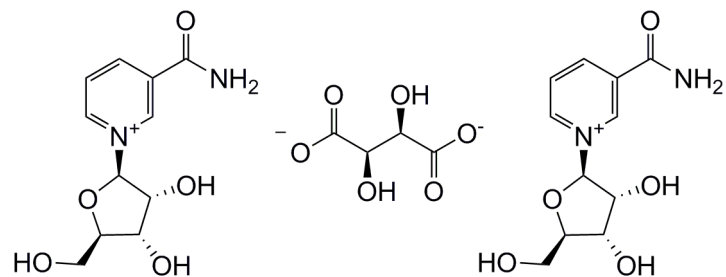


**Example 7: NR L-tartrate**  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ , 400 MHz)

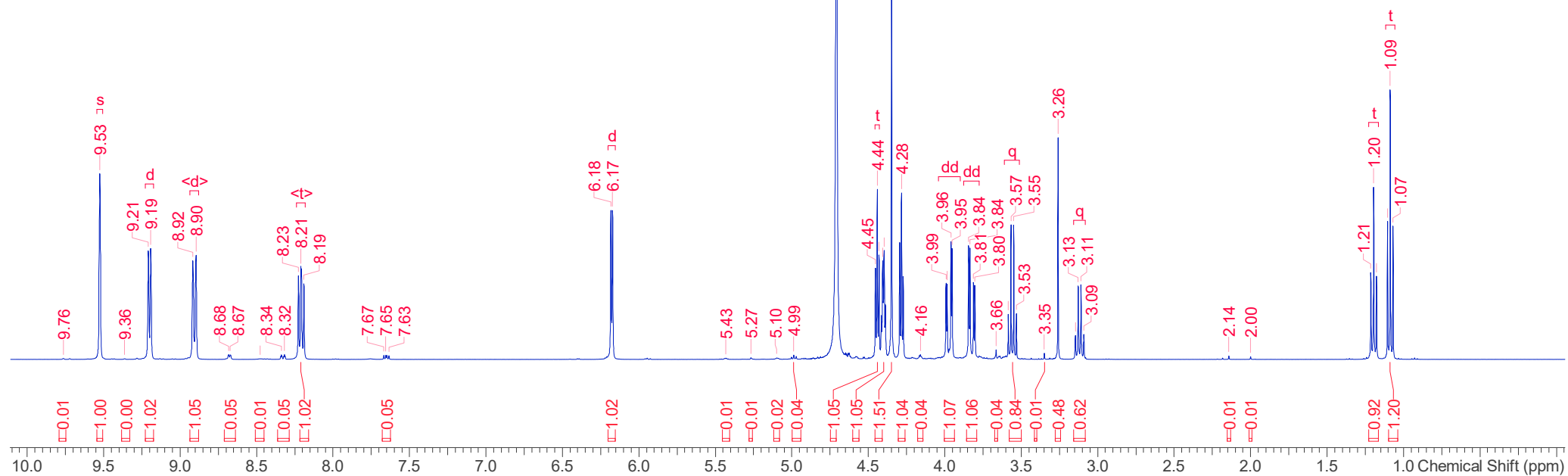
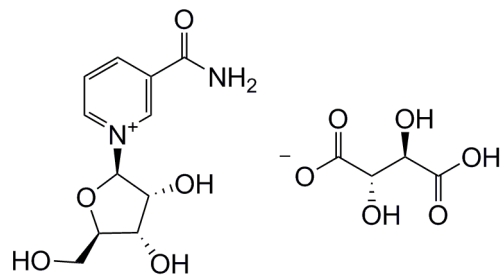




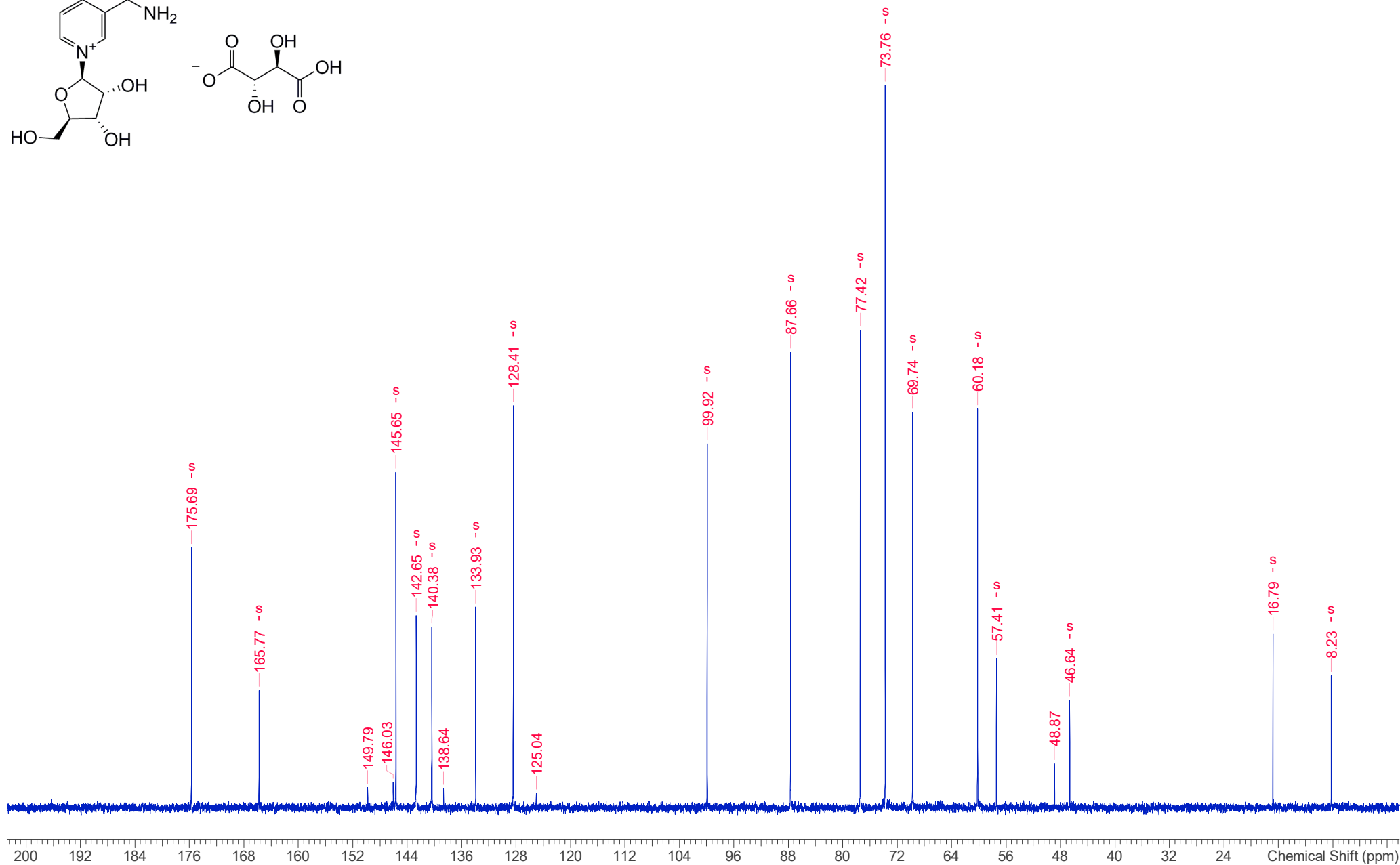
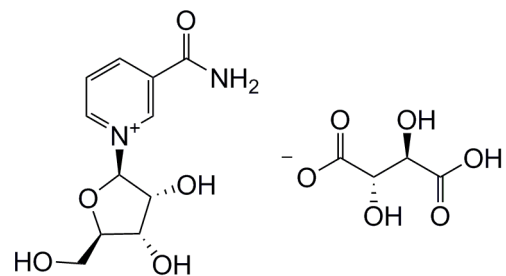
**Example 7: NR L-tartrate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)



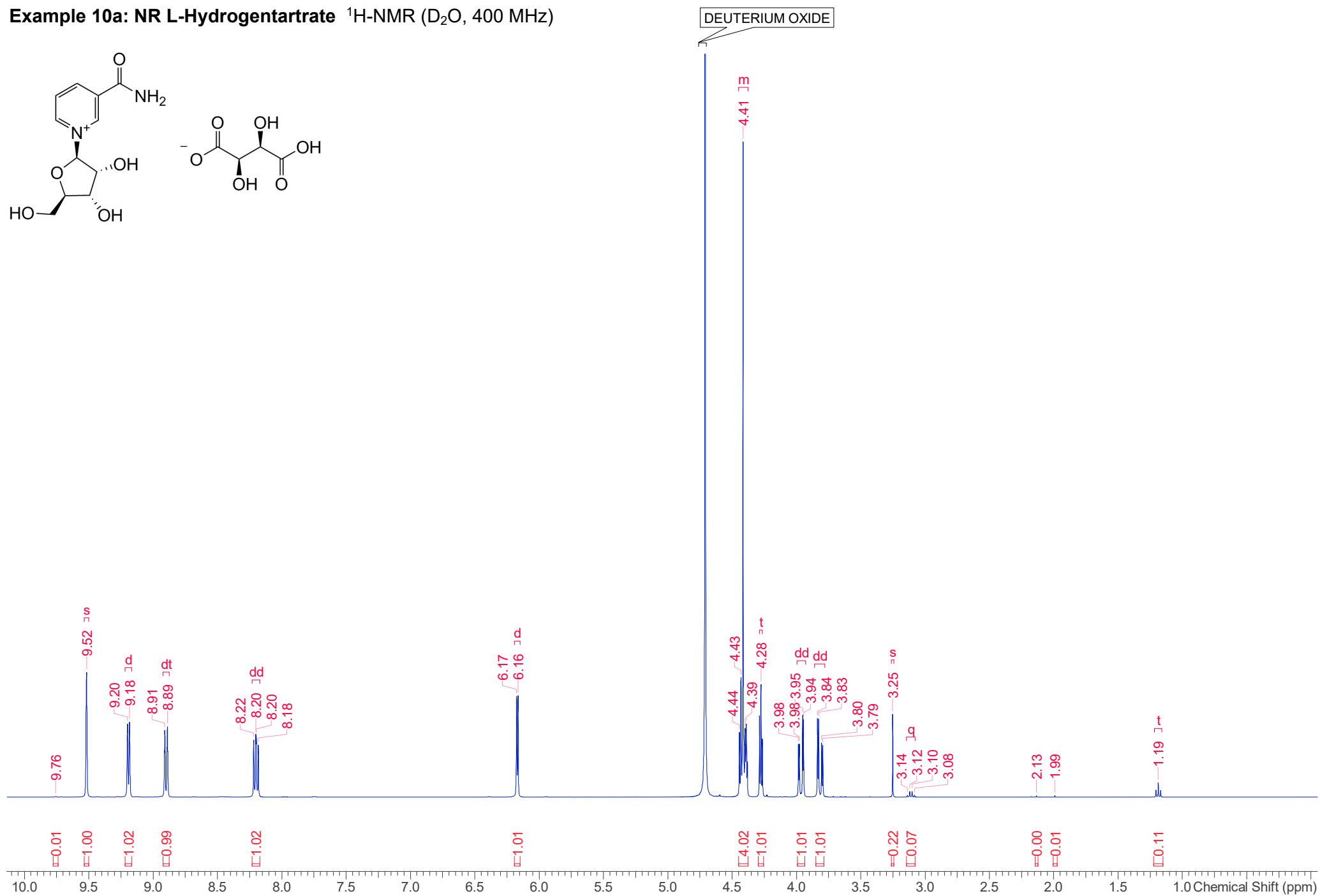
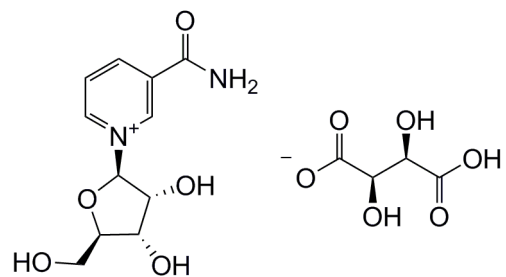
**Example 9: NR meso-Hydrogentartrate**  $^1\text{H}$ -NMR ( $\text{D}_2\text{O}$ , 400 MHz)



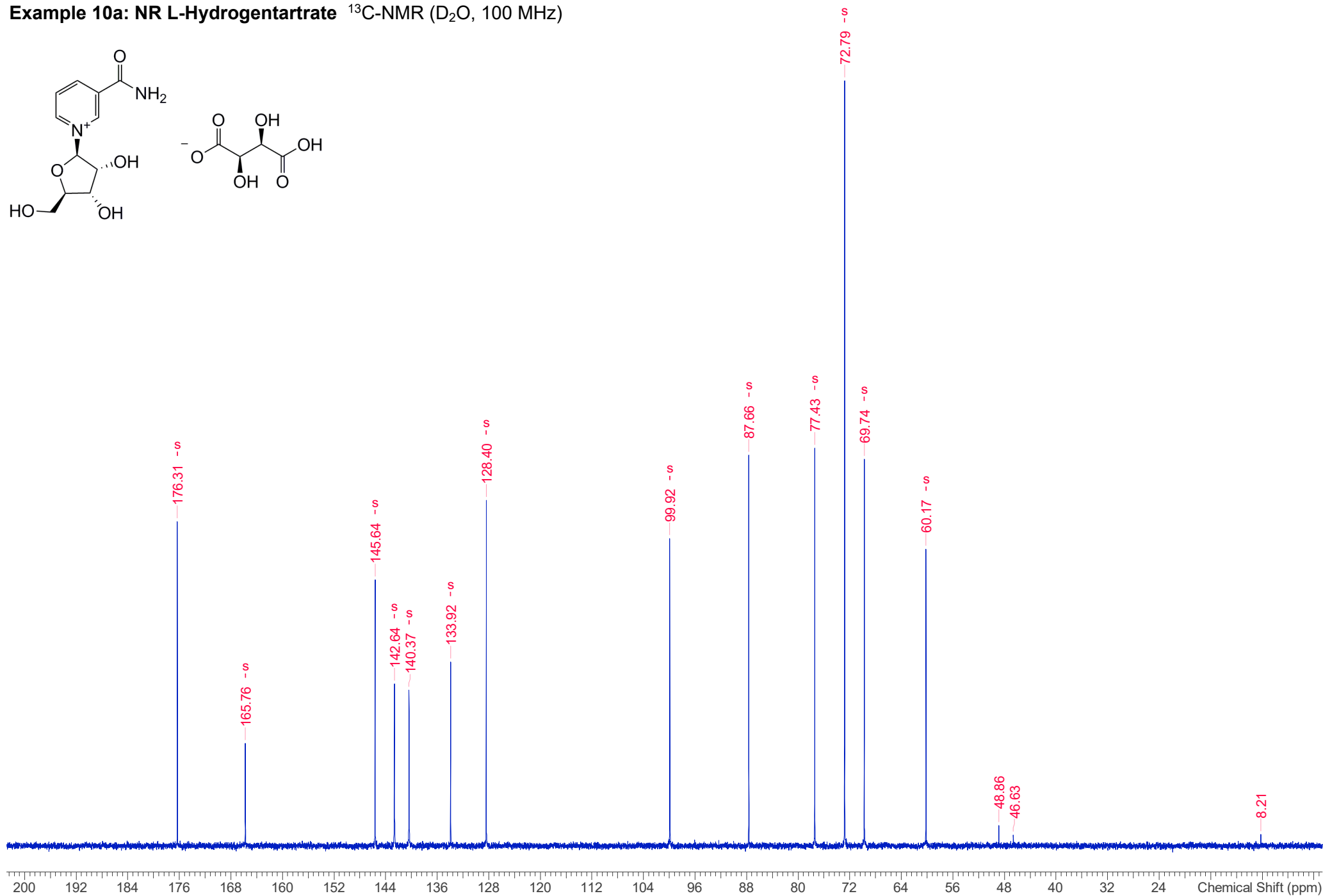
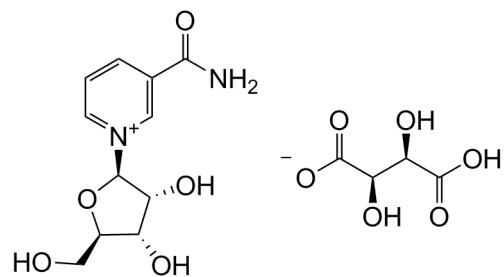
**Example 9: NR meso-Hydrogentartrate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)



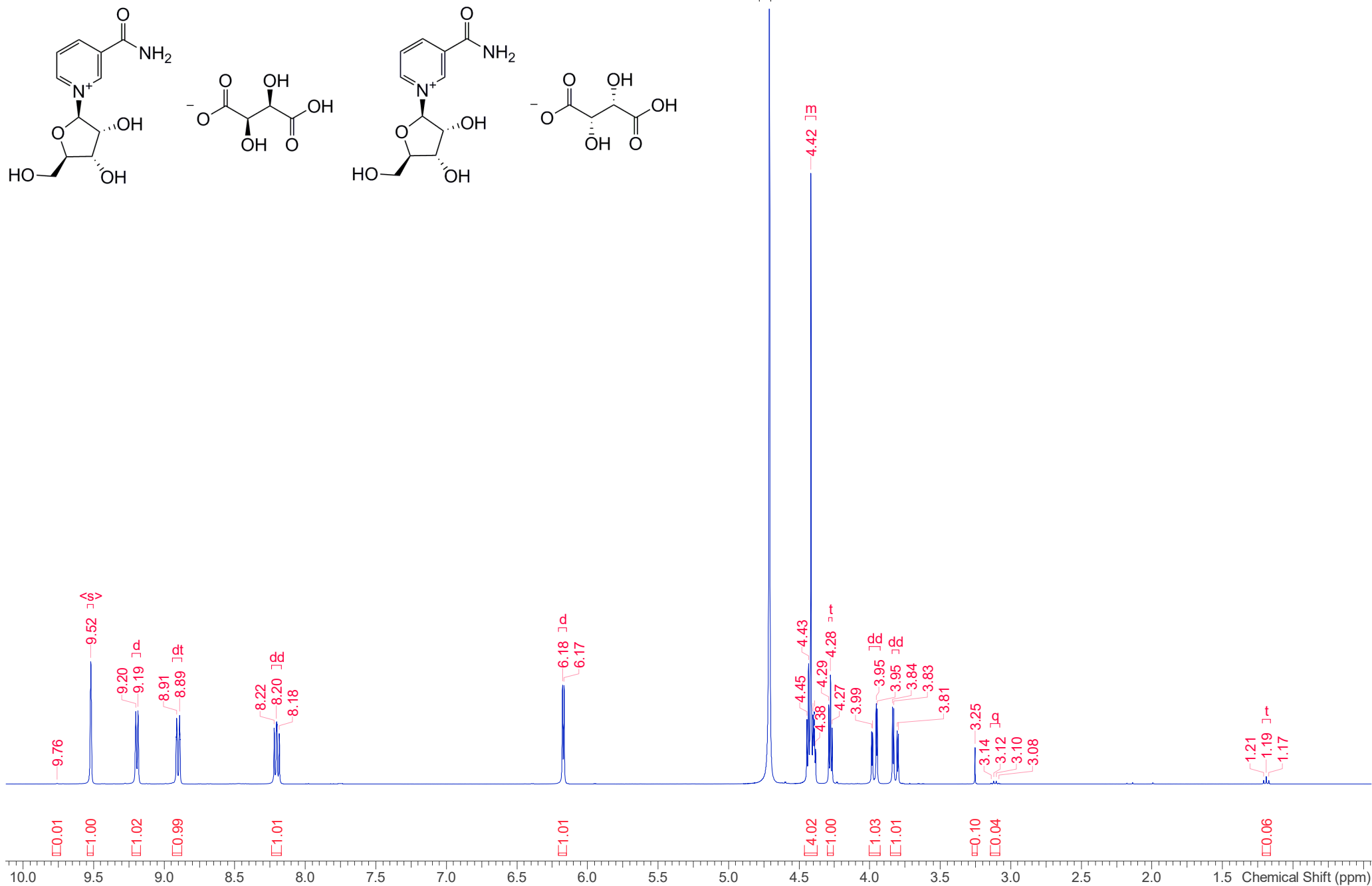
**Example 10a: NR L-Hydrogentartrate**  $^1\text{H}$ -NMR ( $\text{D}_2\text{O}$ , 400 MHz)



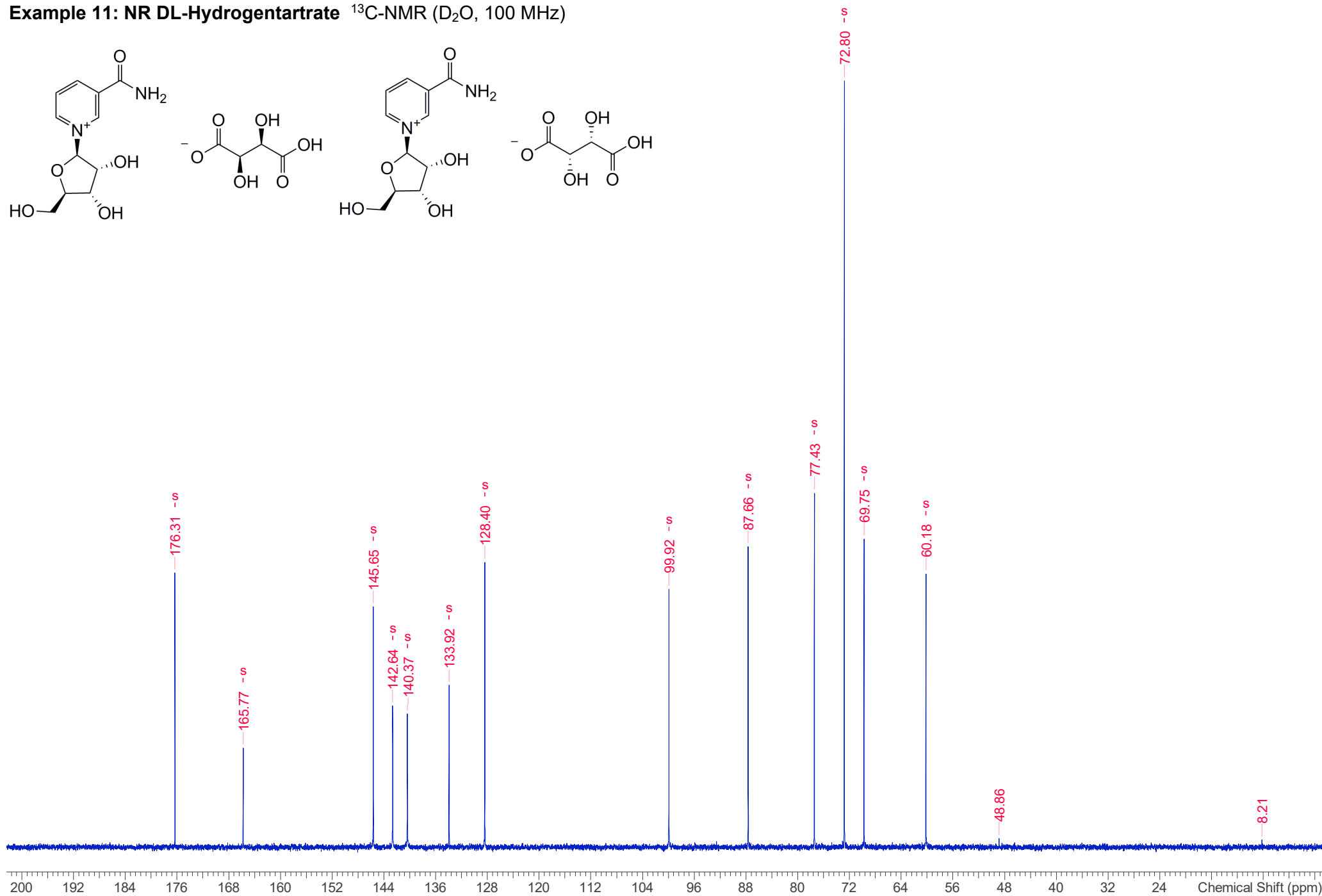
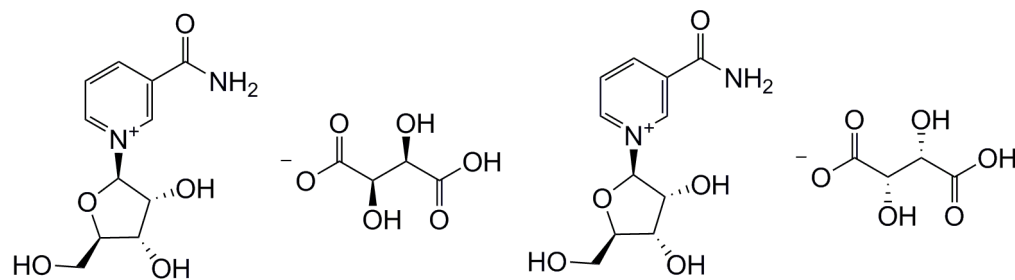
**Example 10a: NR L-Hydrogentartrate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)



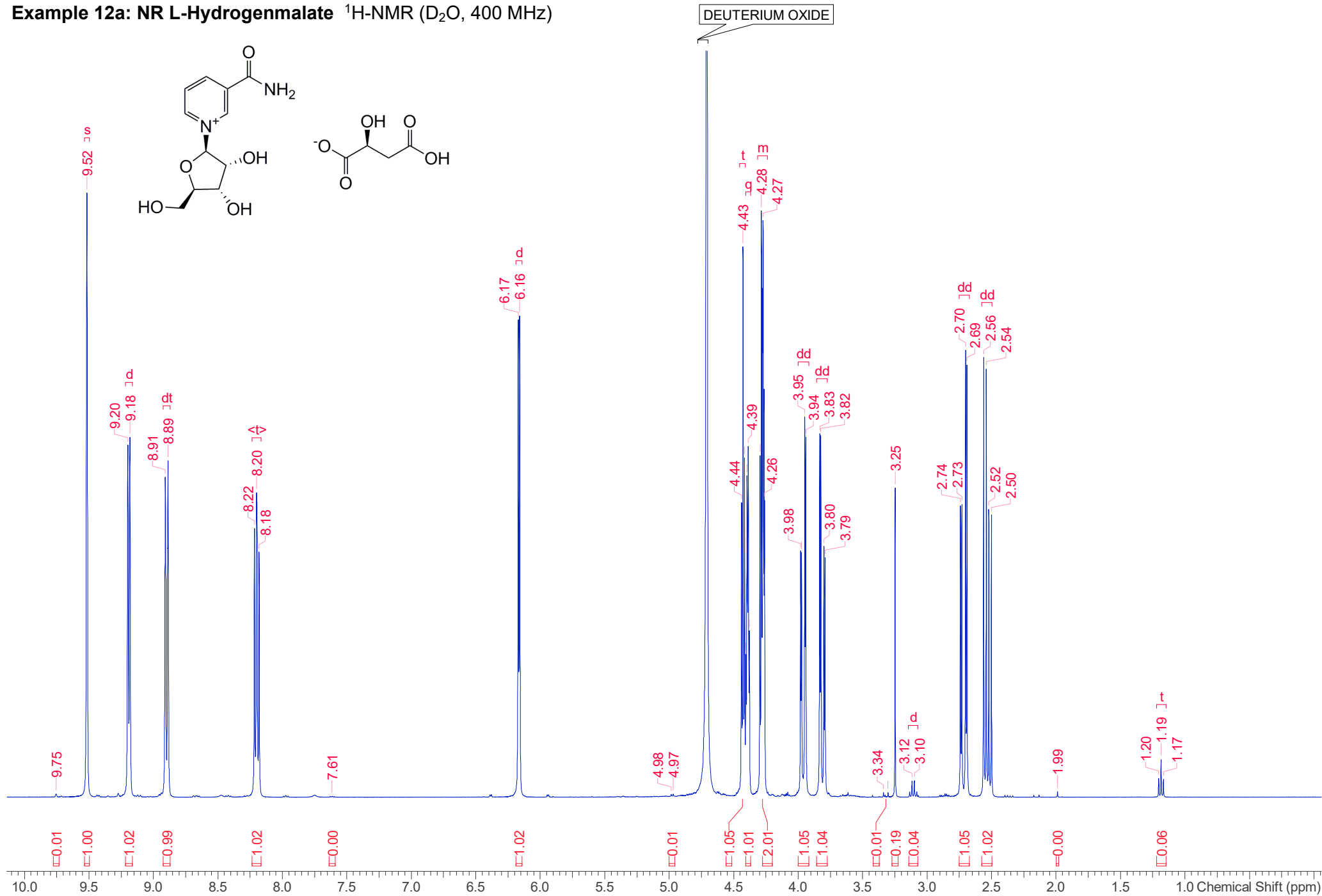
**Example 11: NR DL-Hydrogentartrate**  $^1\text{H}$ -NMR ( $\text{D}_2\text{O}$ , 400 MHz)



**Example 11: NR DL-Hydrogentartrate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)

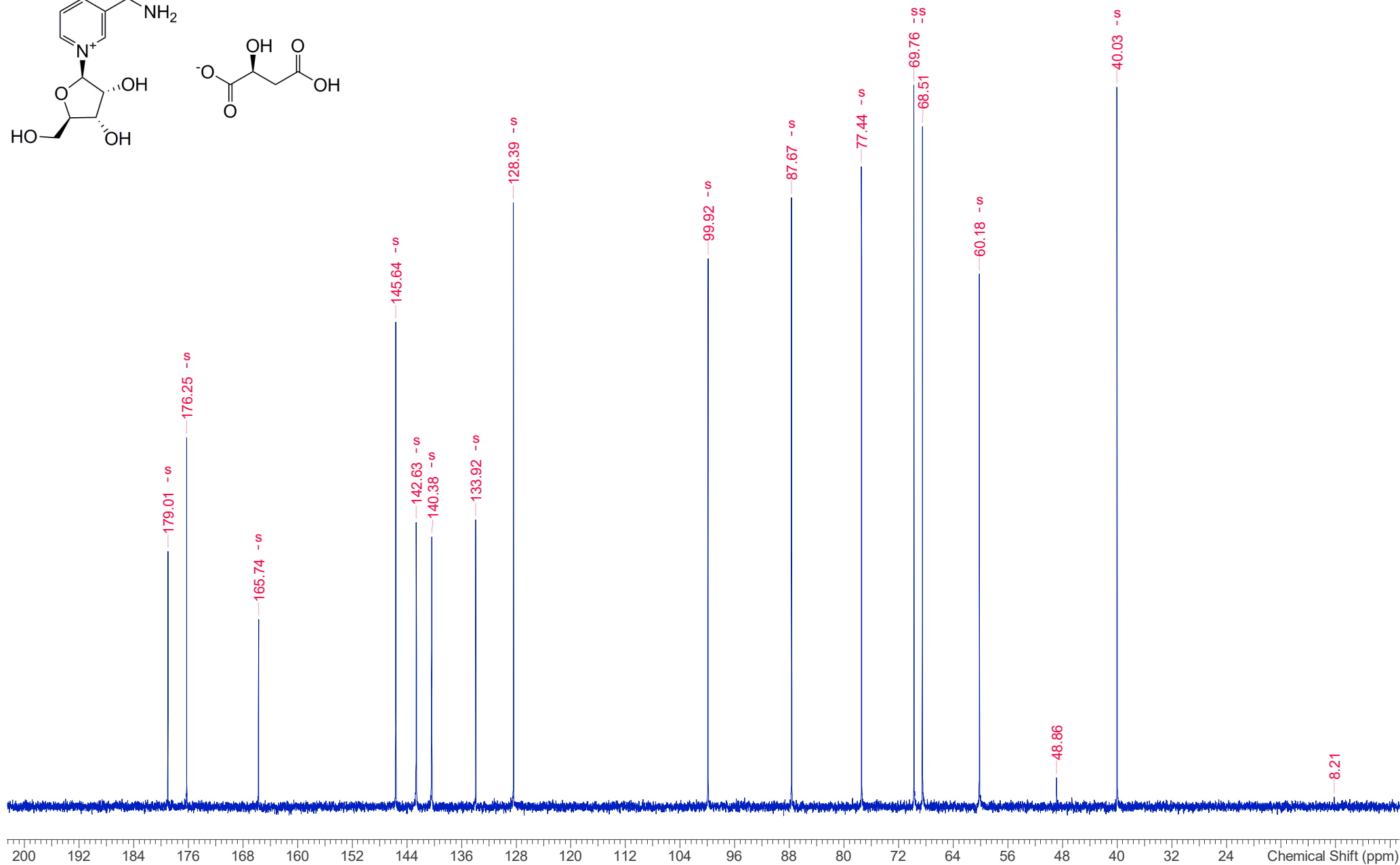
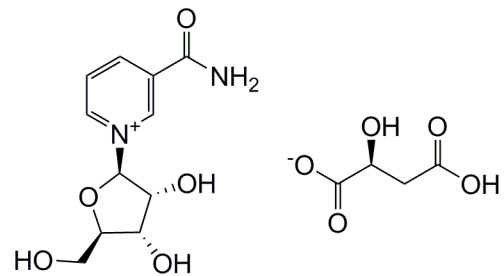


Example 12a: NR L-Hydrogenmalate <sup>1</sup>H-NMR (D<sub>2</sub>O, 400 MHz)

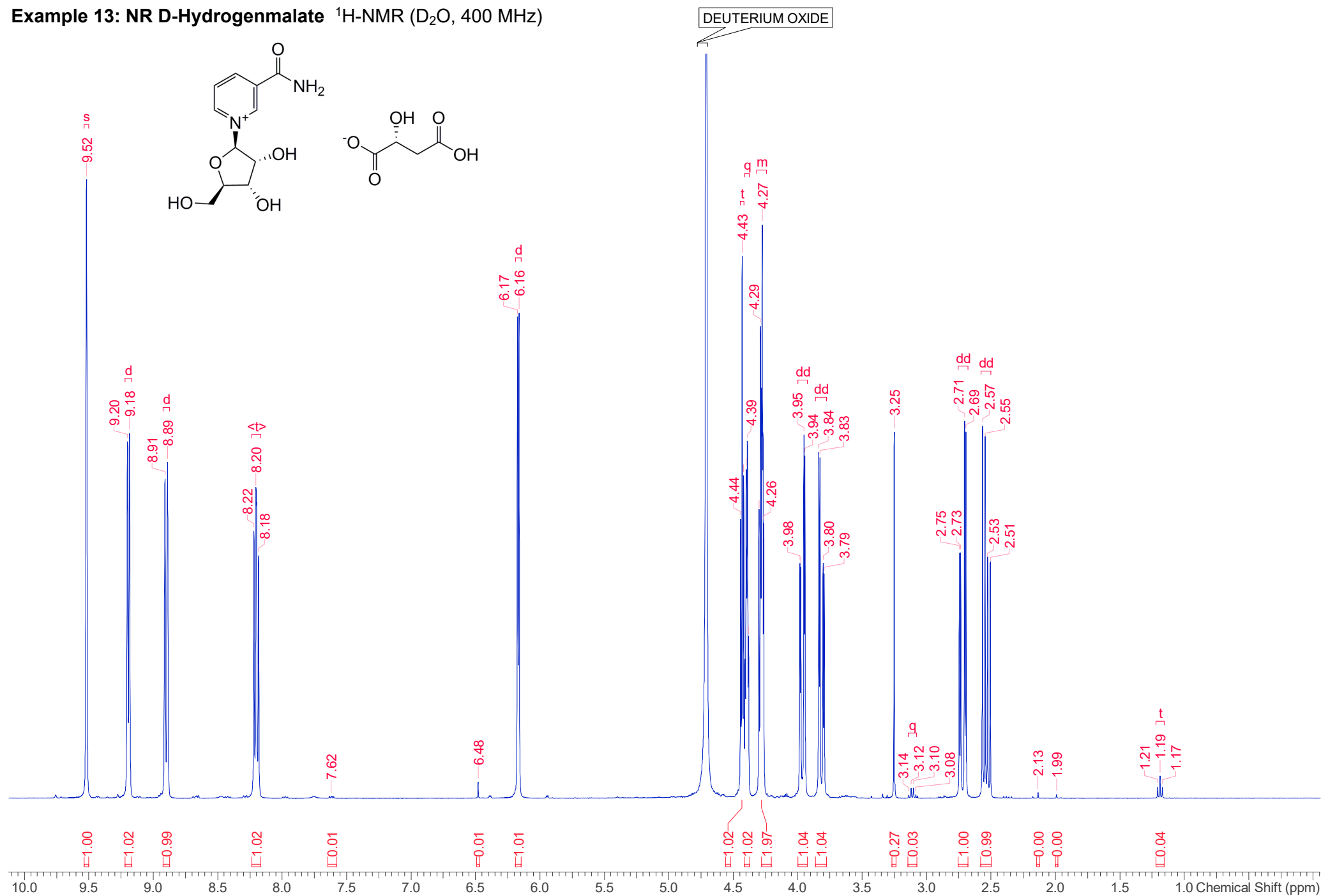
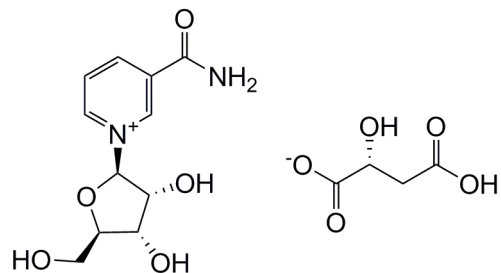




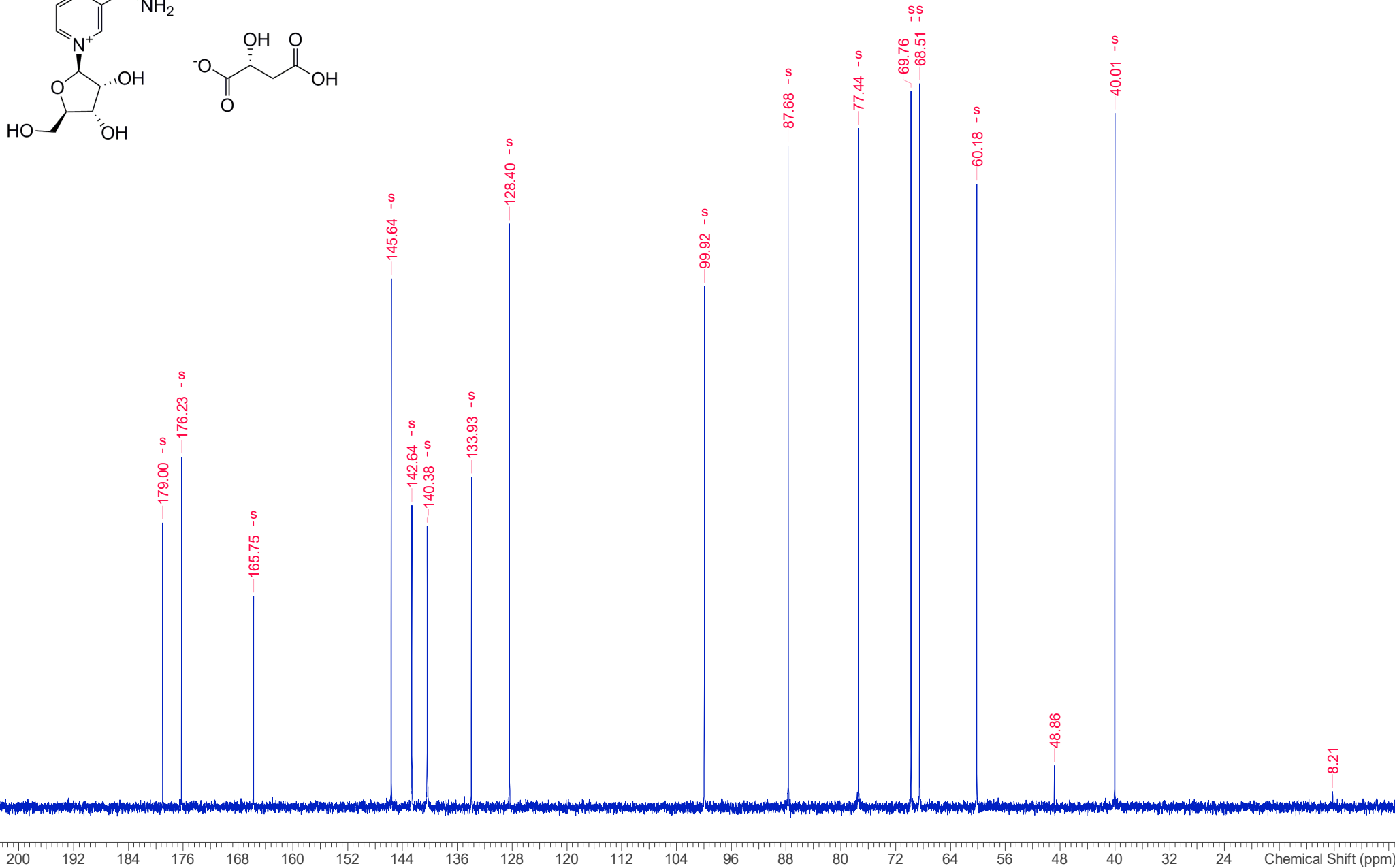
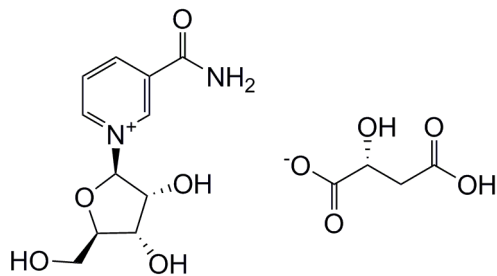
**Example 12a: NR L-Hydrogenmalate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)



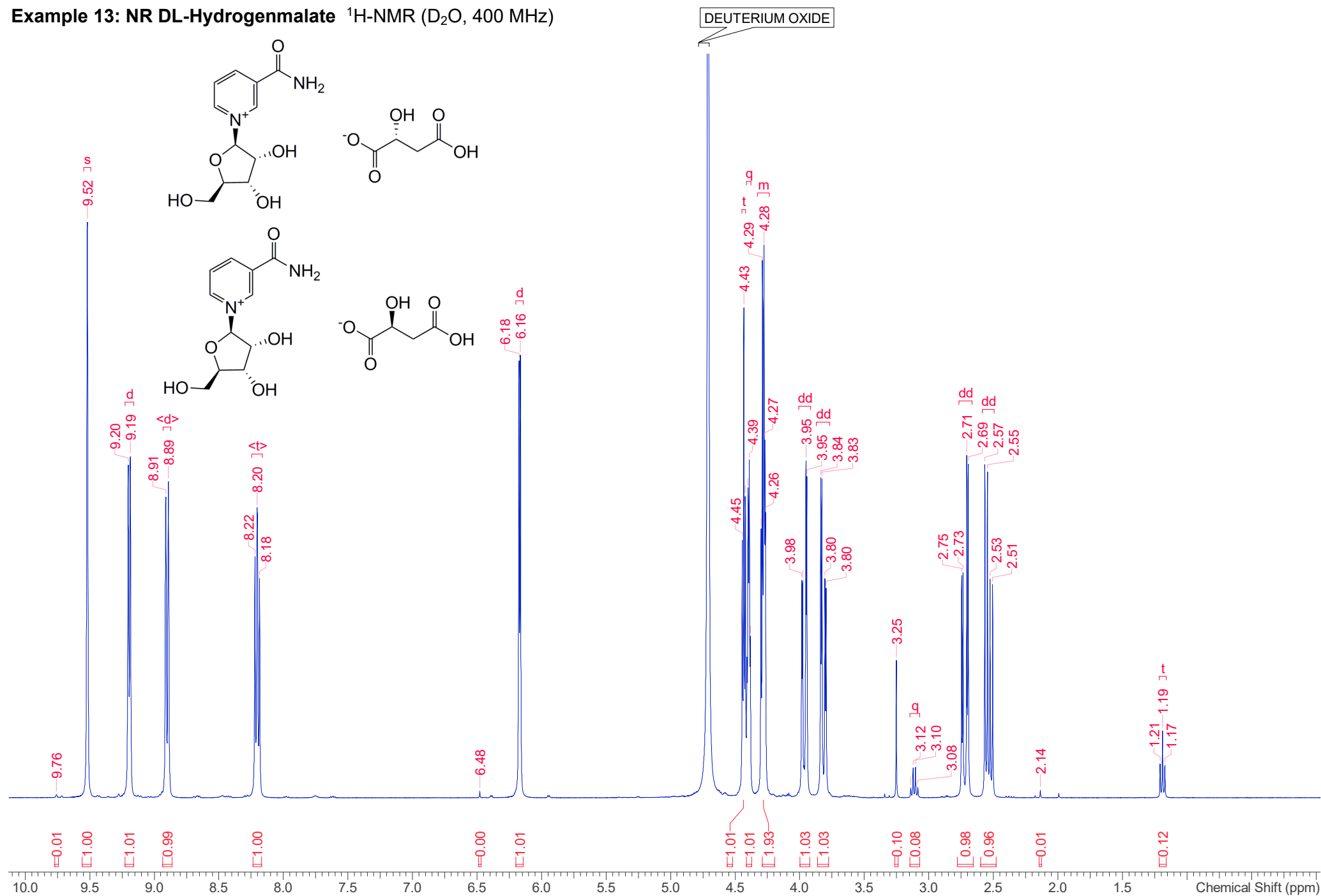
**Example 13: NR D-Hydrogenmalate**  $^1\text{H}$ -NMR ( $\text{D}_2\text{O}$ , 400 MHz)



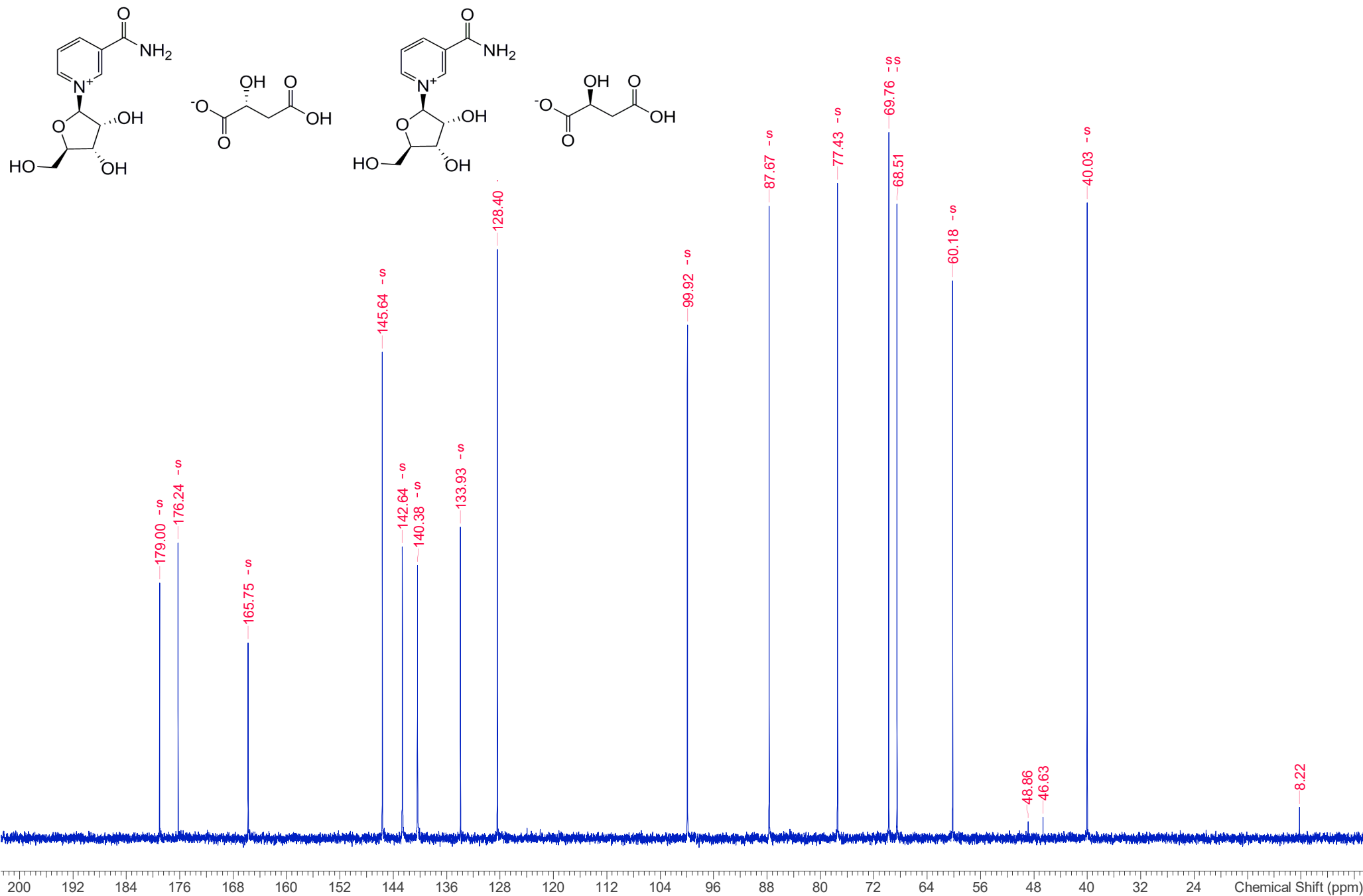
Example 13: NR D-Hydrogenmalate <sup>13</sup>C-NMR (D<sub>2</sub>O, 100 MHz)



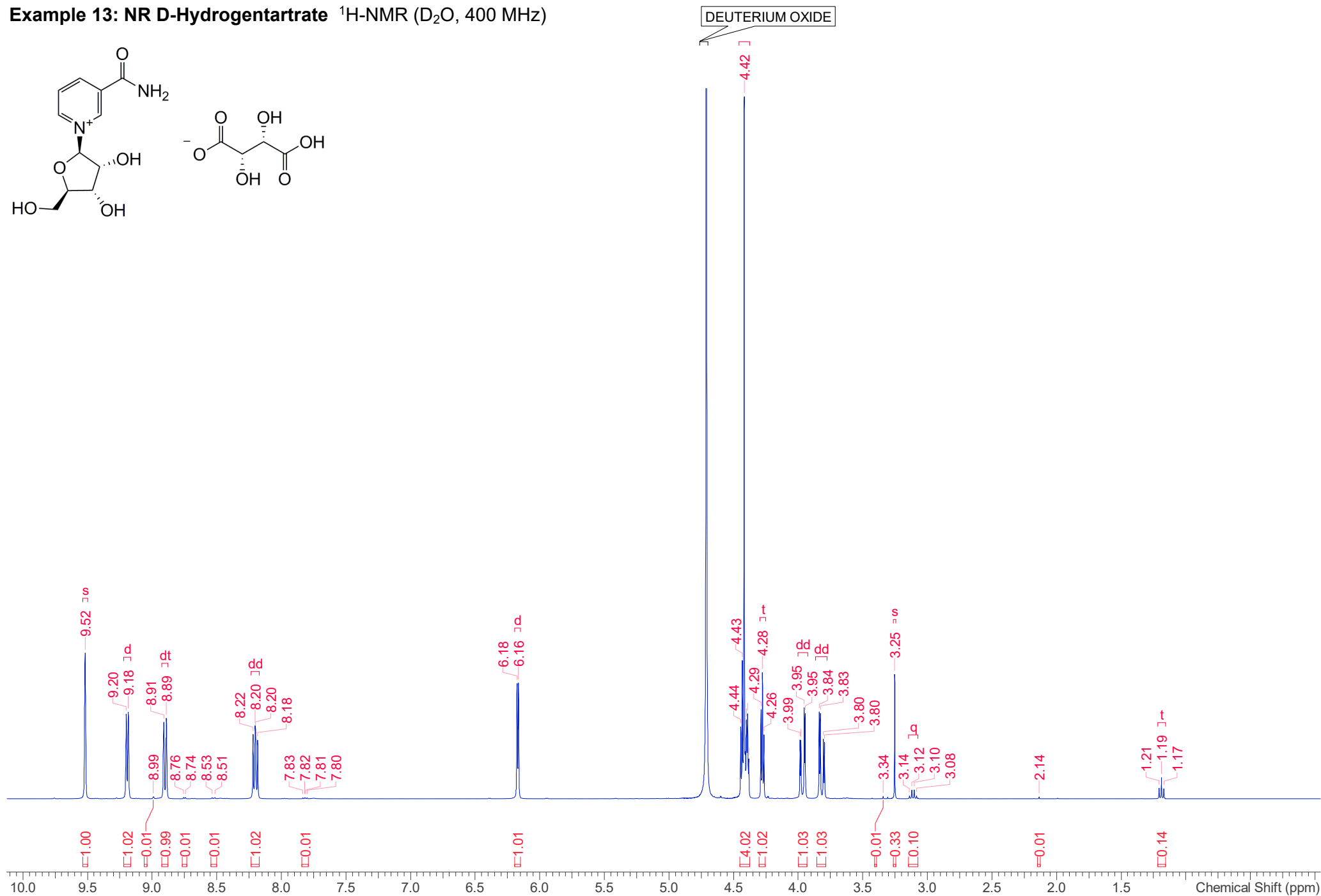
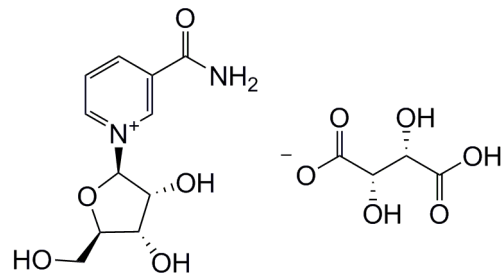
**Example 13: NR DL-Hydrogenmalate**  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ , 400 MHz)



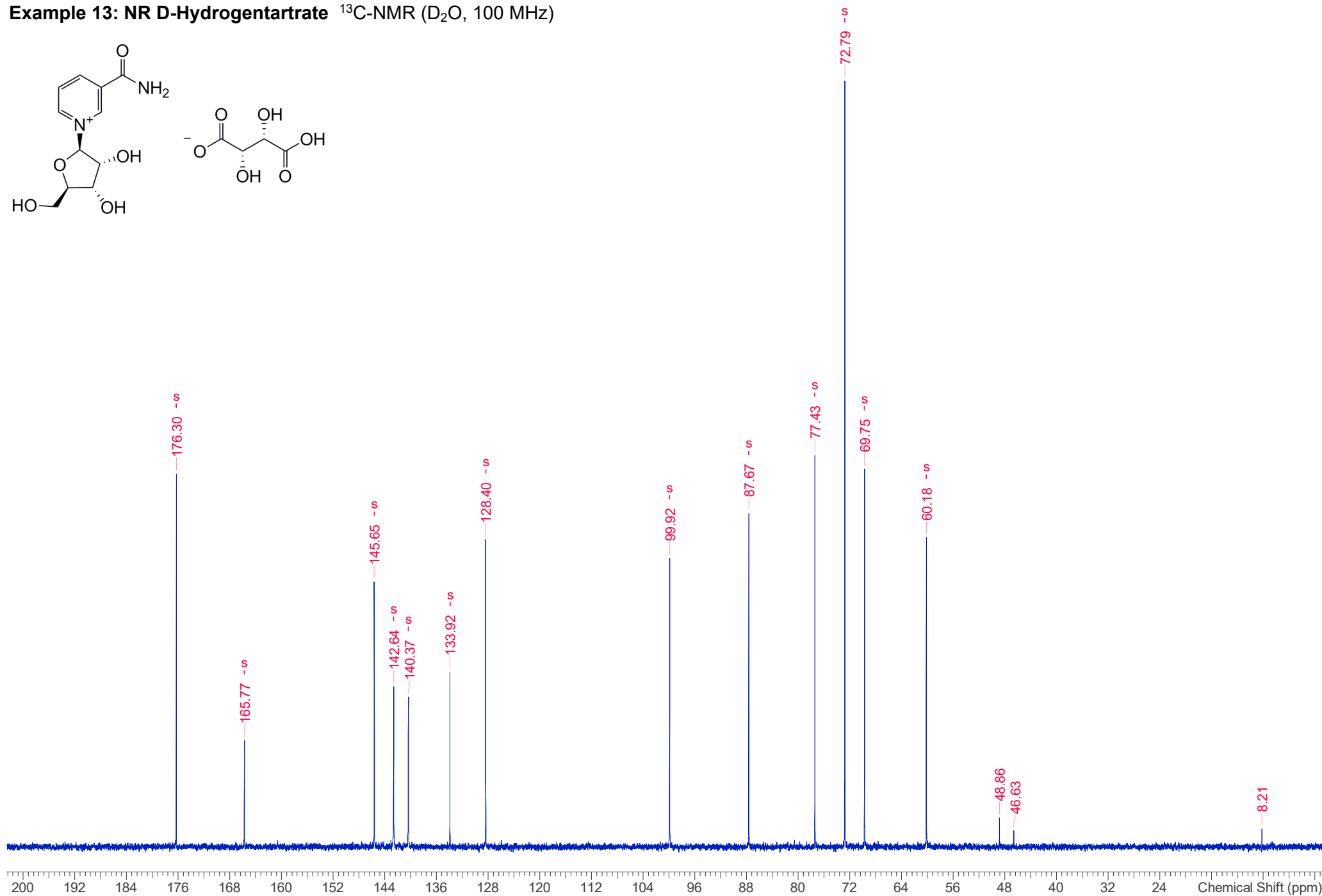
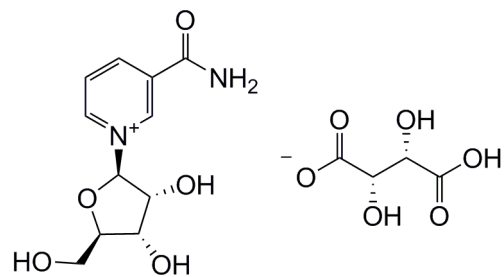
**Example 13: NR DL-Hydrogenmalate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)



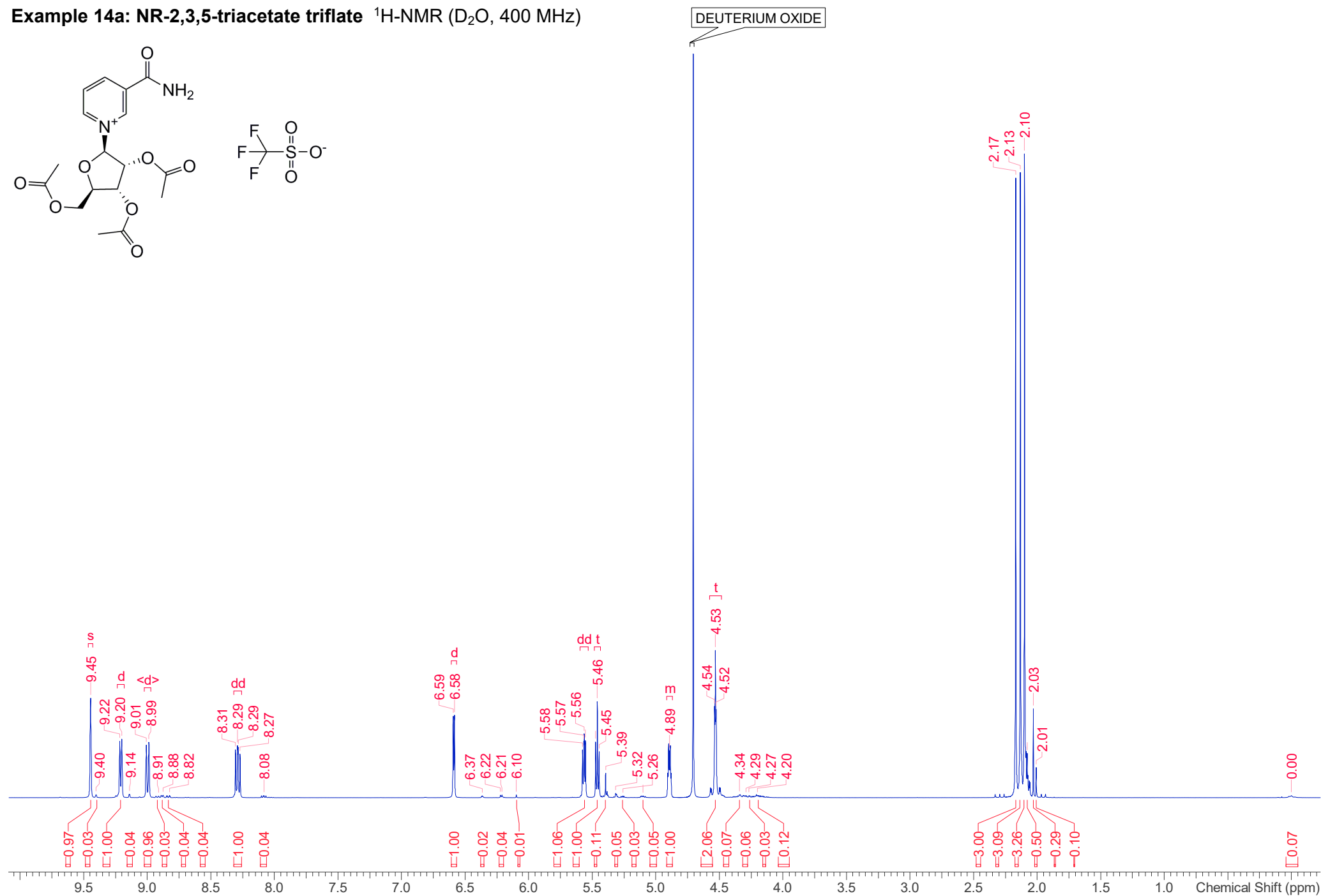
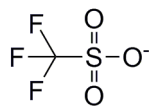
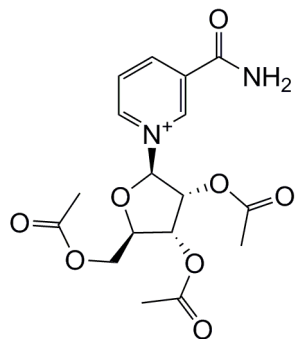
**Example 13: NR D-Hydrogentartrate**  $^1\text{H}$ -NMR ( $\text{D}_2\text{O}$ , 400 MHz)



**Example 13: NR D-Hydrogentartrate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)

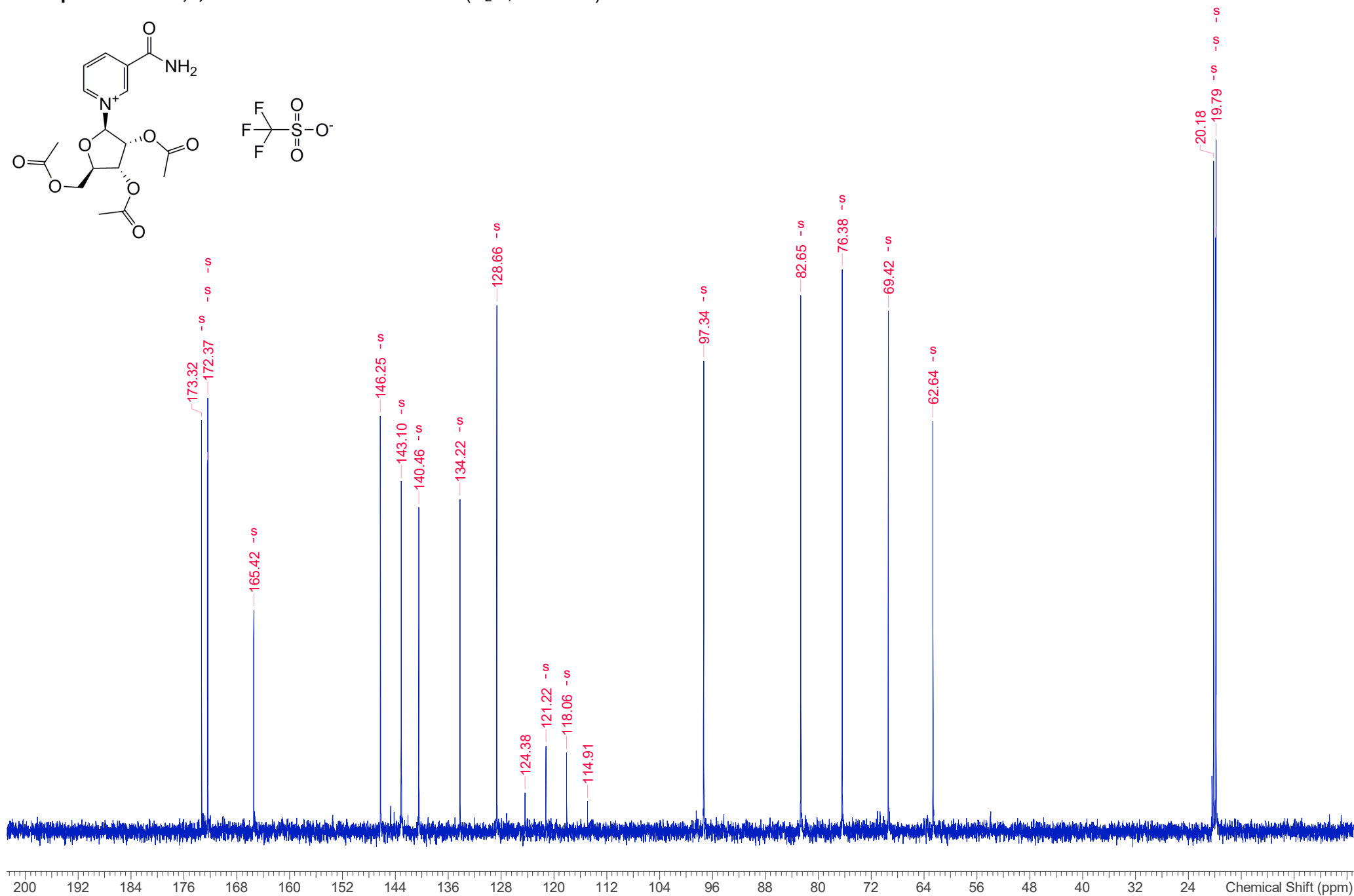
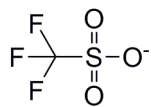
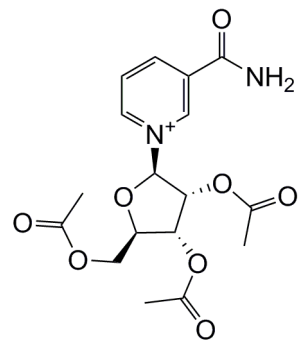


**Example 14a: NR-2,3,5-triacetate triflate**  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ , 400 MHz)

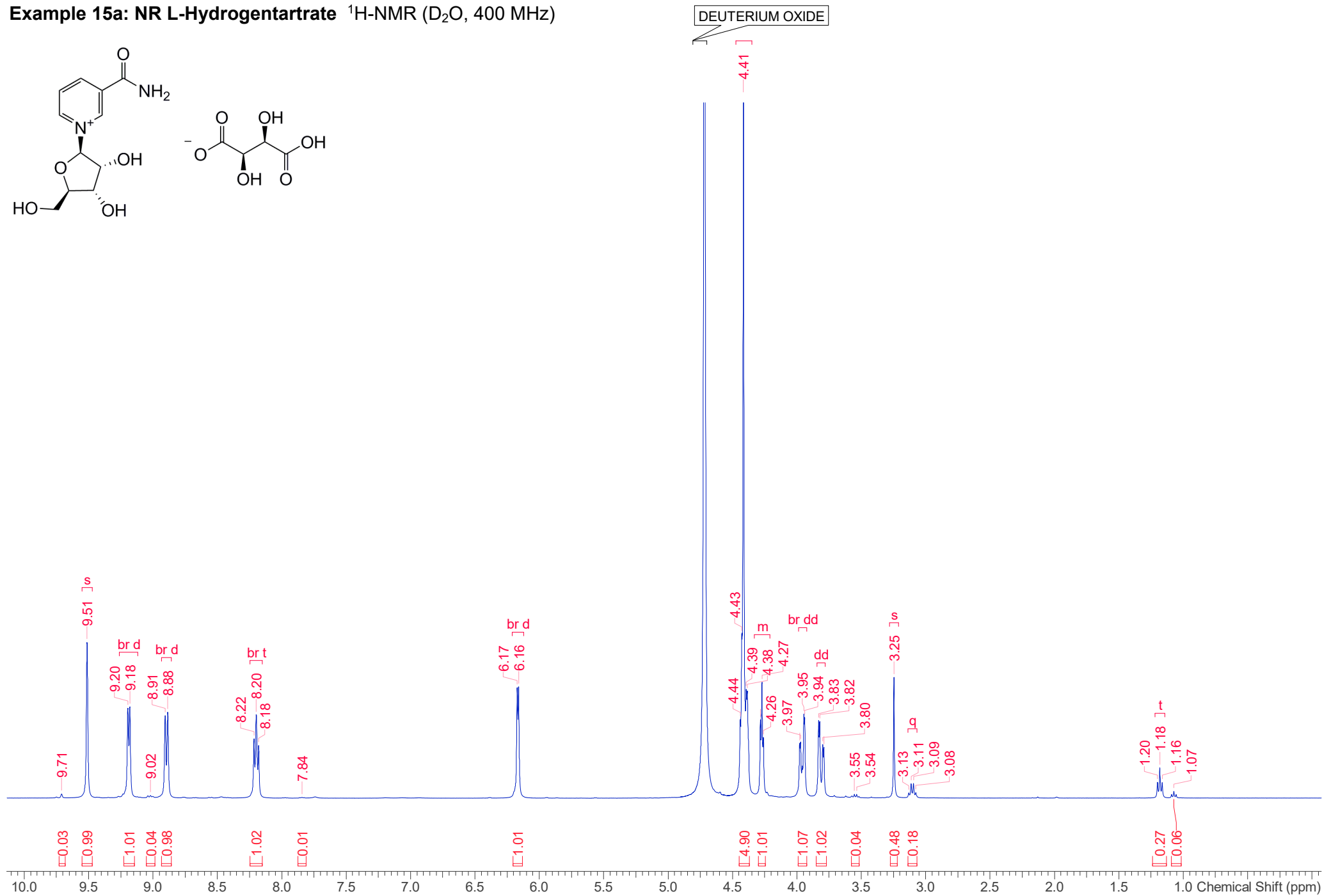
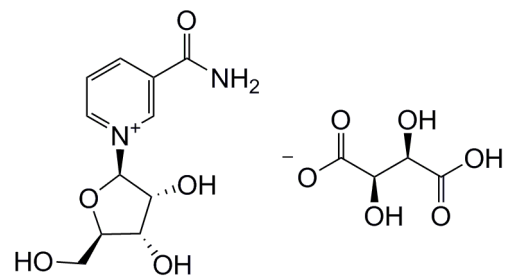




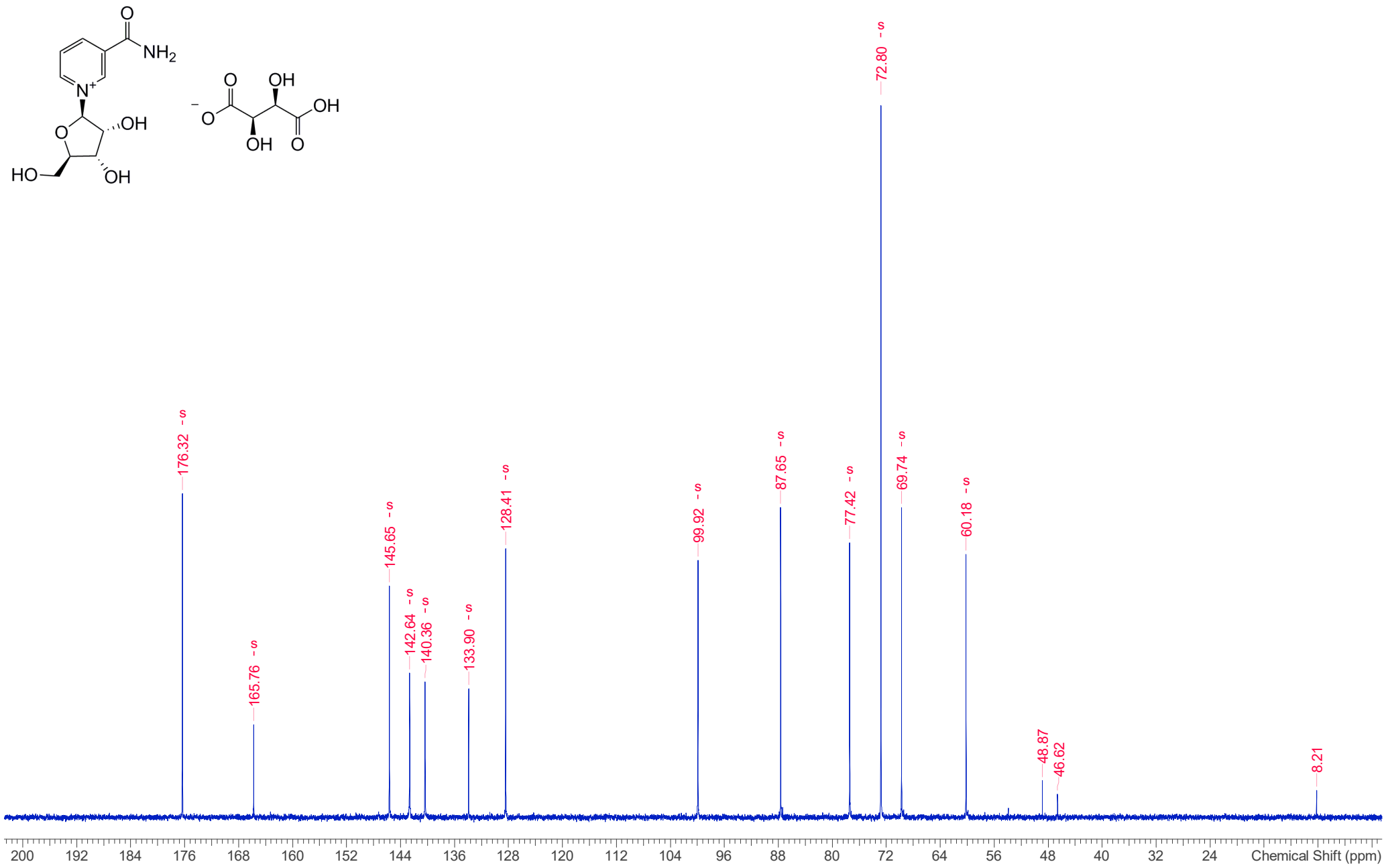
**Example 14a: NR-2,3,5-triacetate triflate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)



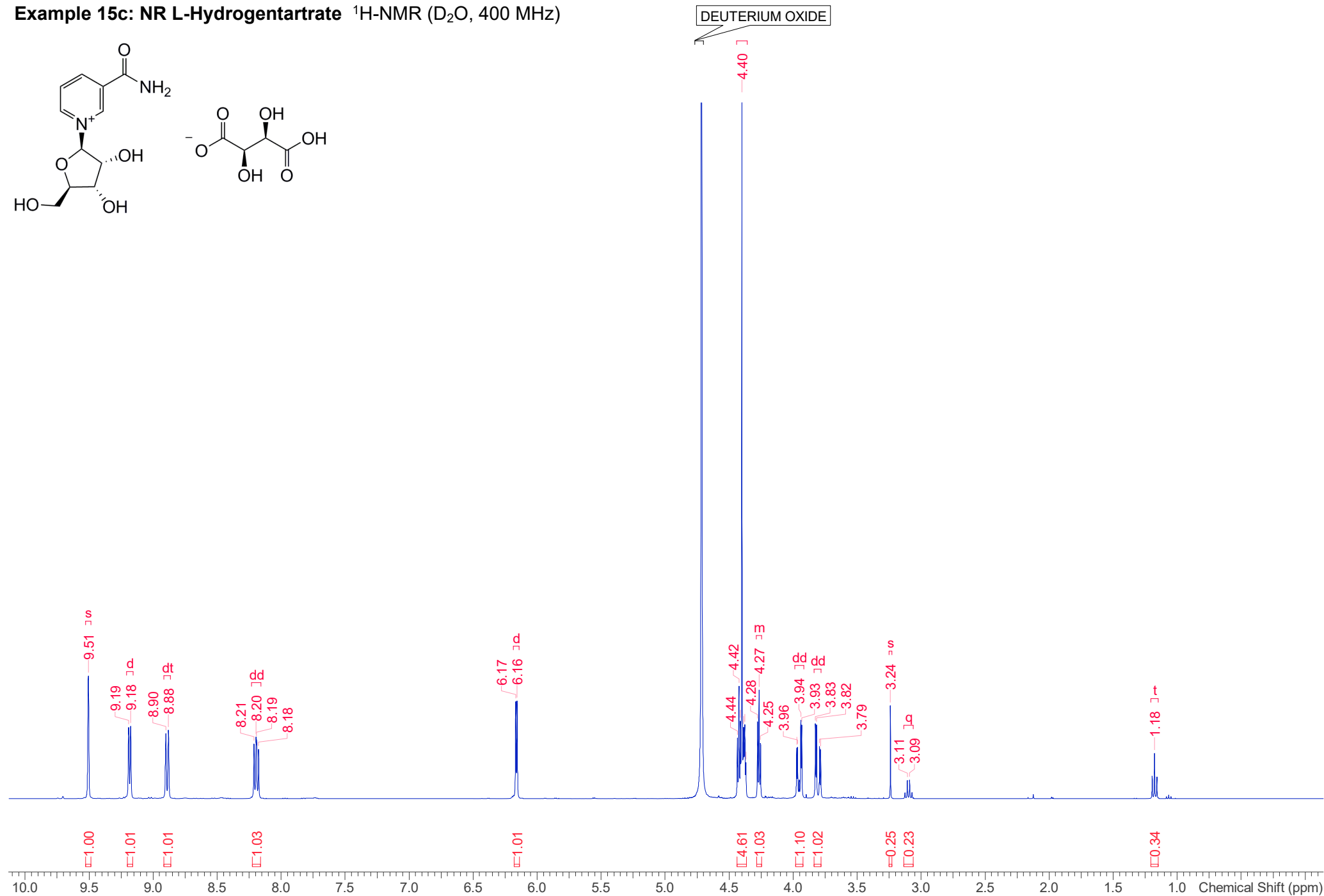
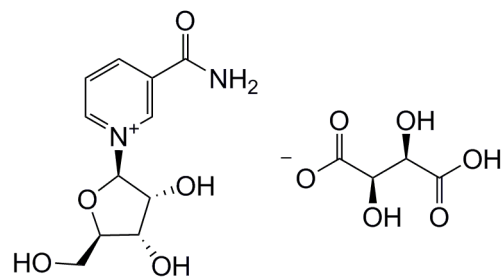
**Example 15a: NR L-Hydrogentartrate**  $^1\text{H}$ -NMR ( $\text{D}_2\text{O}$ , 400 MHz)



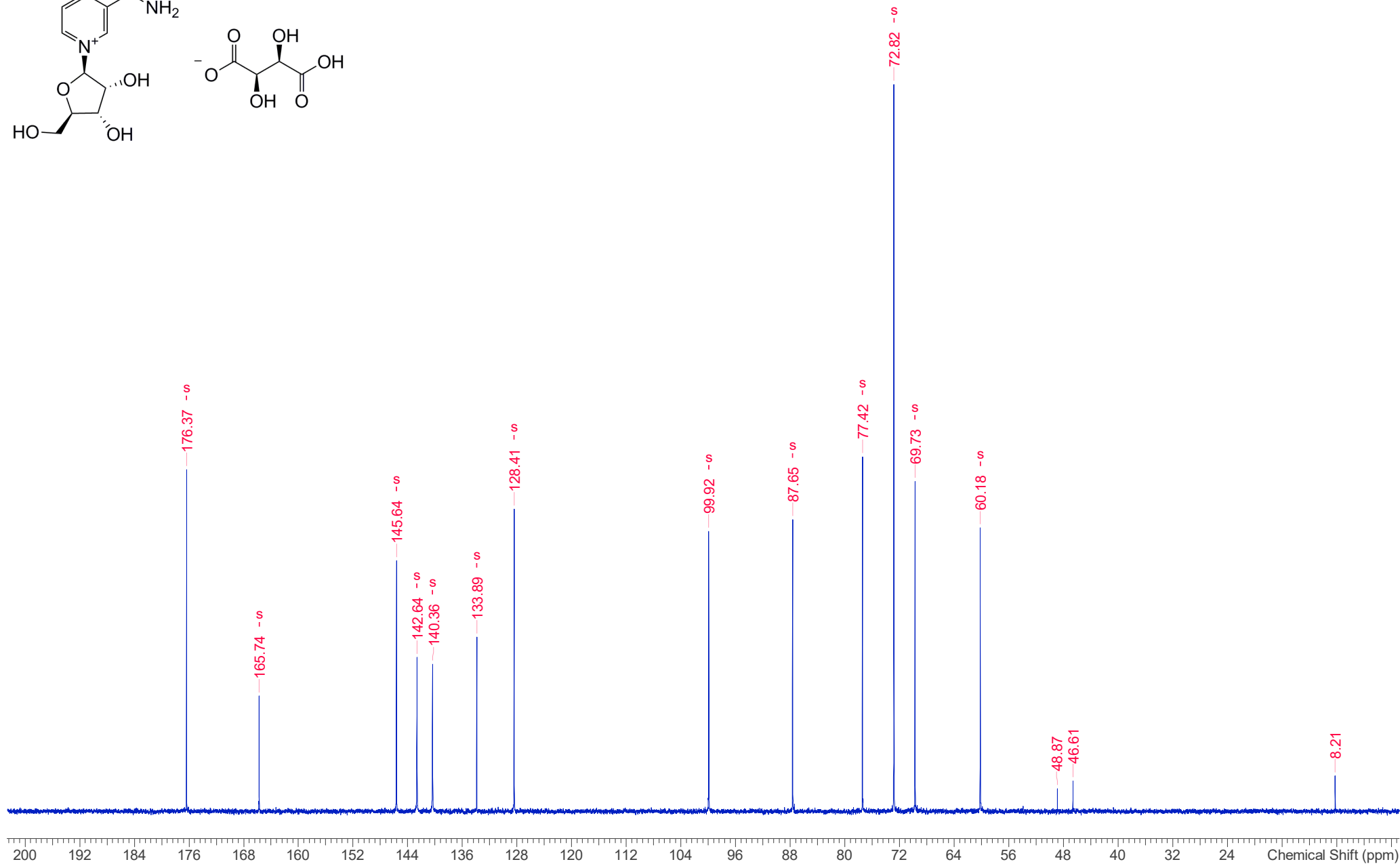
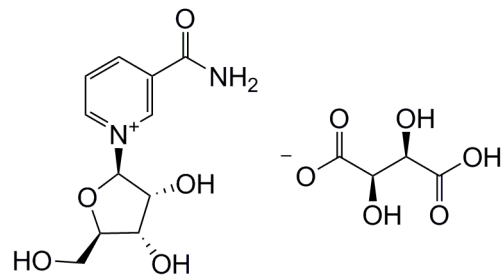
Example 15a: NR L-Hydrogentartrate <sup>13</sup>C-NMR (D<sub>2</sub>O, 100 MHz)



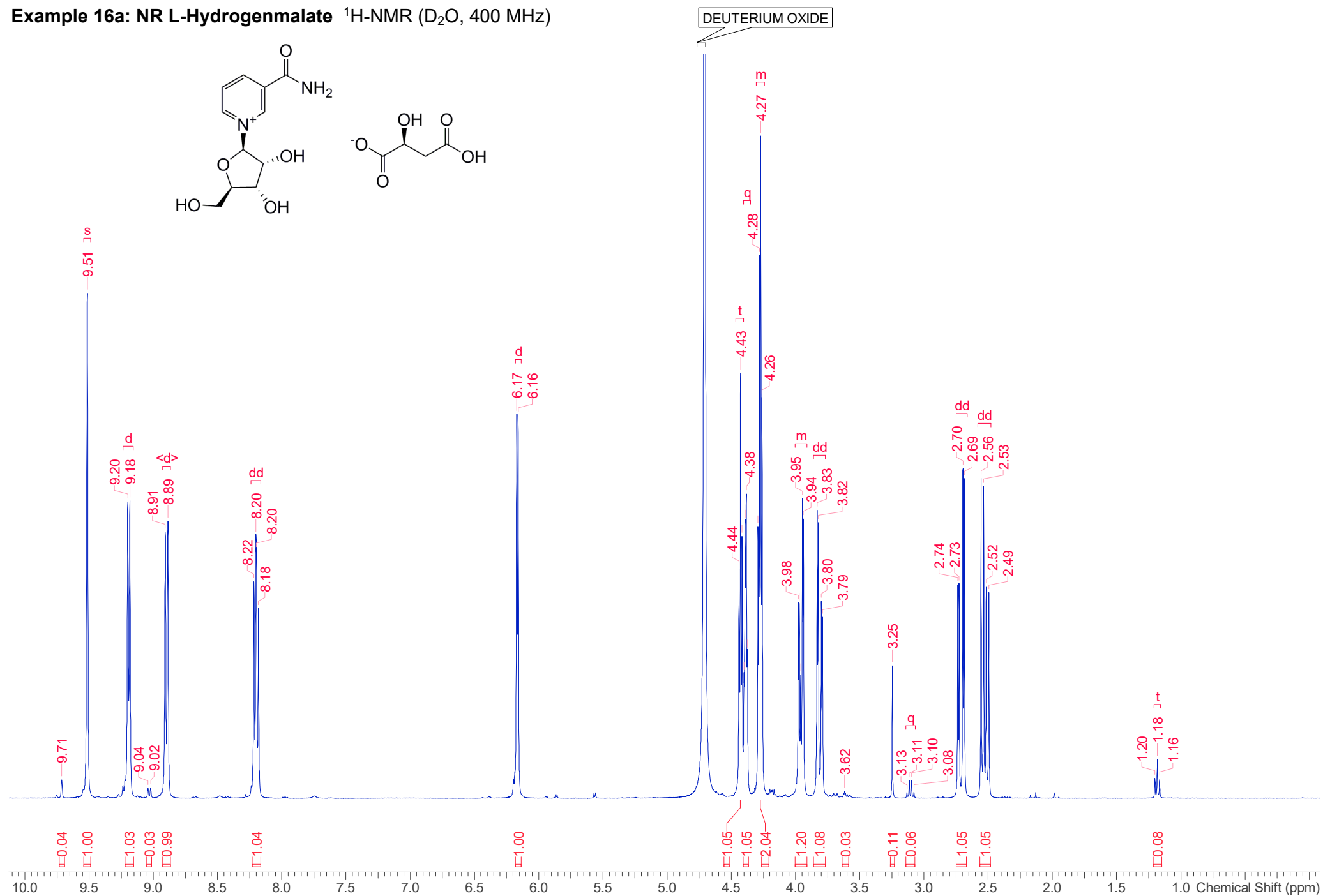
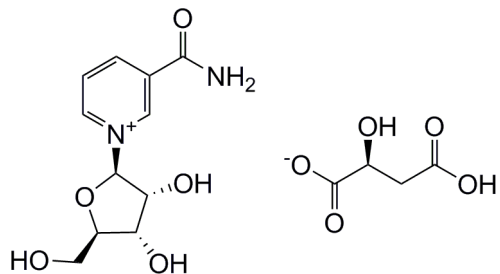
**Example 15c: NR L-Hydrogentartrate**  $^1\text{H}$ -NMR ( $\text{D}_2\text{O}$ , 400 MHz)



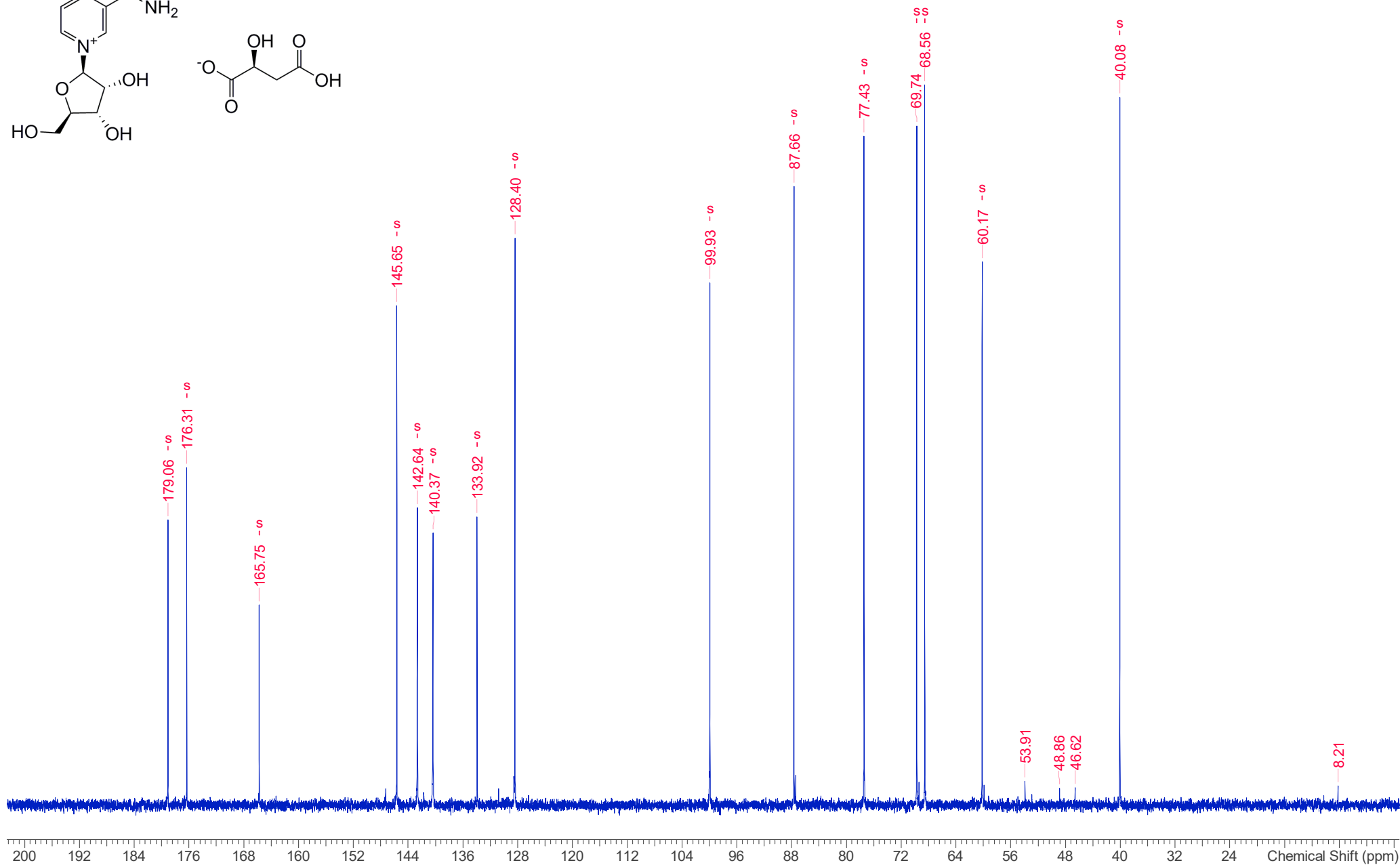
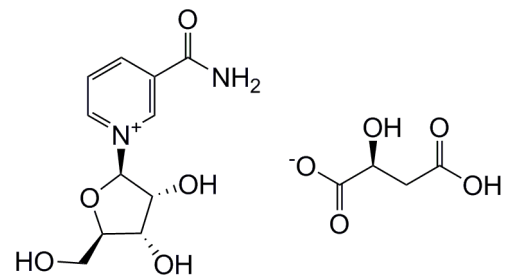
**Example 15c: NR L-Hydrogentartrate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)



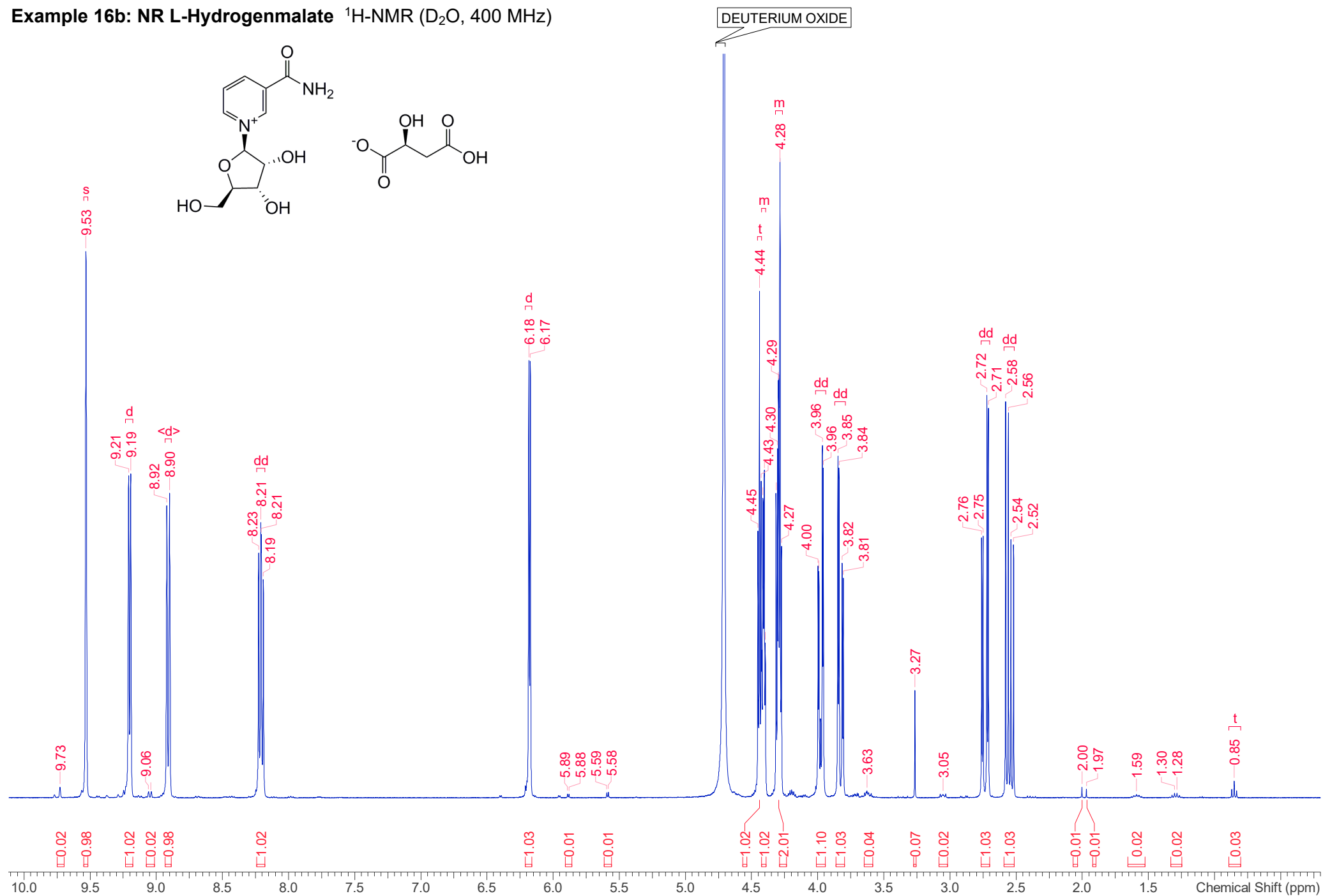
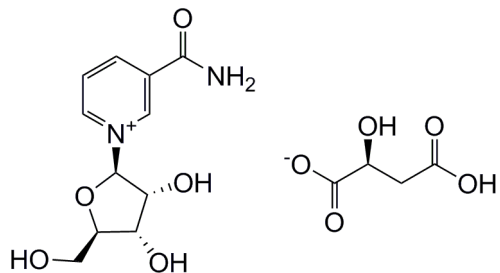
**Example 16a: NR L-Hydrogenmalate**  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ , 400 MHz)



**Example 16a: NR L-Hydrogenmalate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)

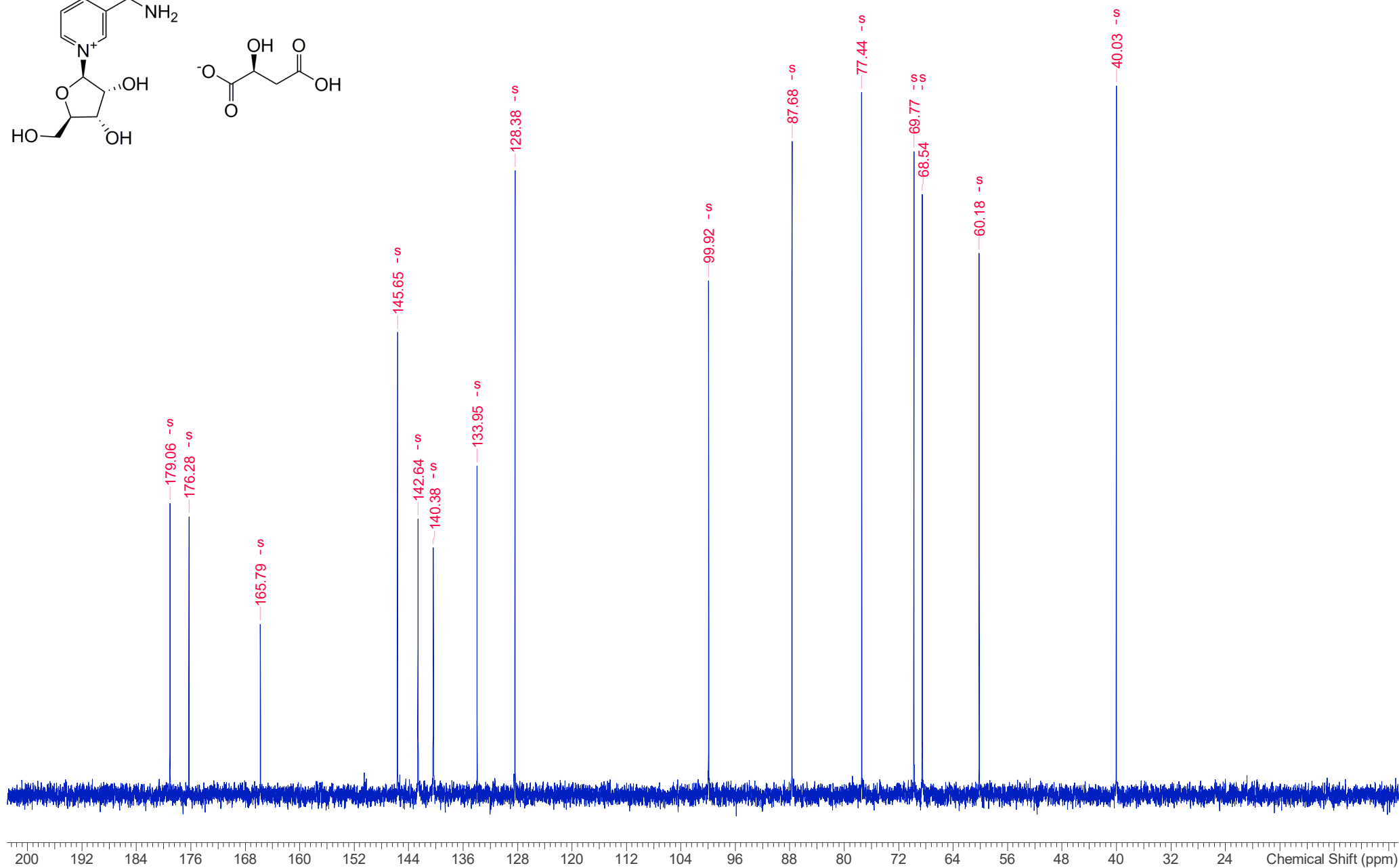
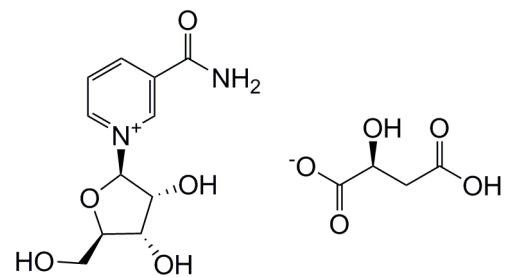


**Example 16b: NR L-Hydrogenmalate**  $^1\text{H}$ -NMR ( $\text{D}_2\text{O}$ , 400 MHz)

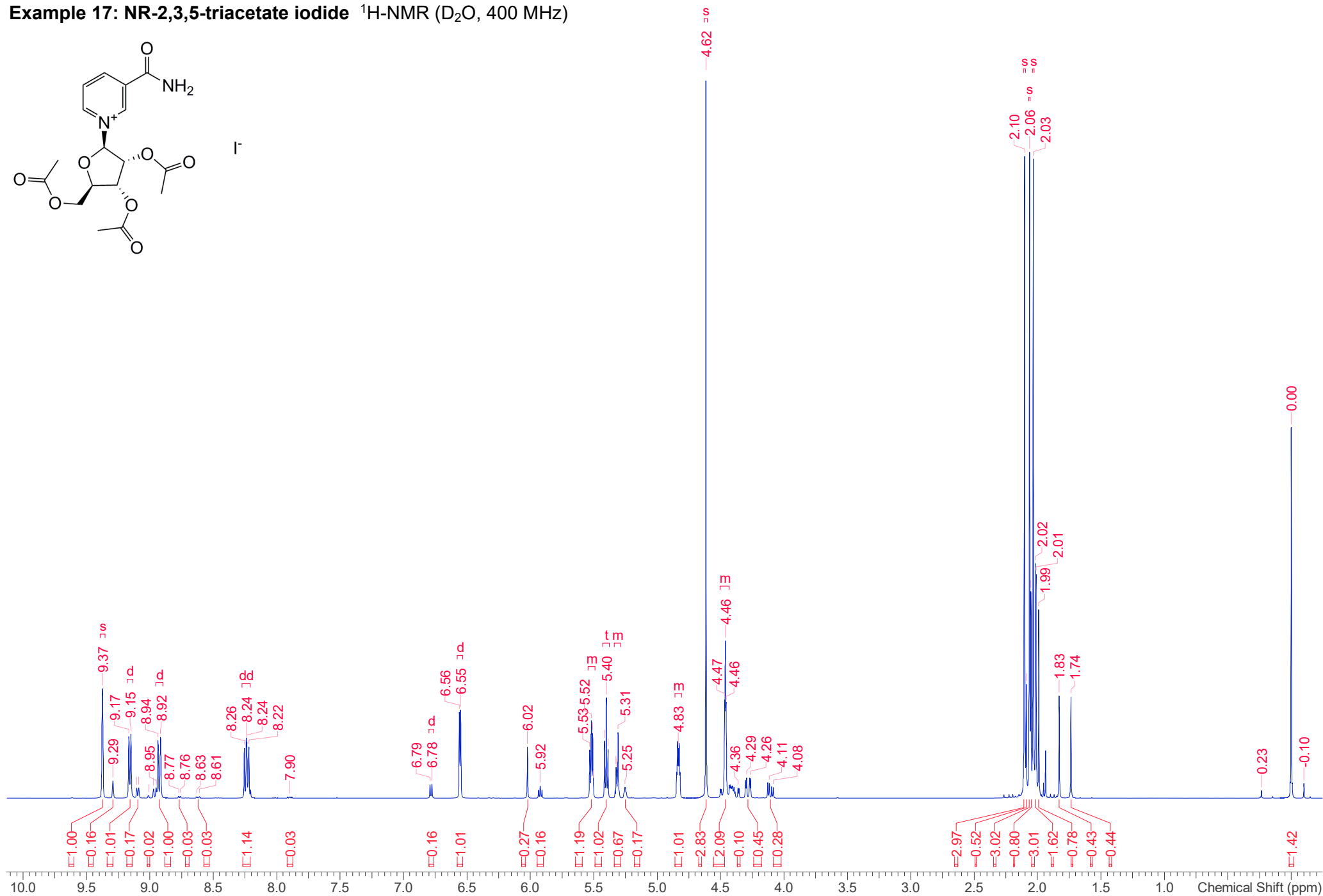
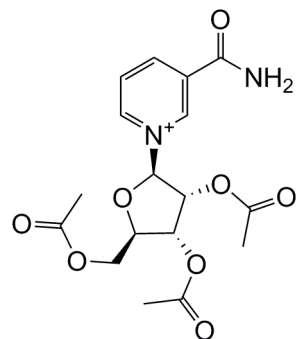




**Example 16b: NR L-Hydrogenmalate**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)



**Example 17: NR-2,3,5-triacetate iodide**  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ , 400 MHz)



**Example 17: NR-2,3,5-triacetate iodide**  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ , 100 MHz)

